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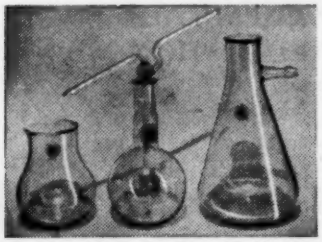

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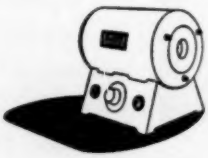

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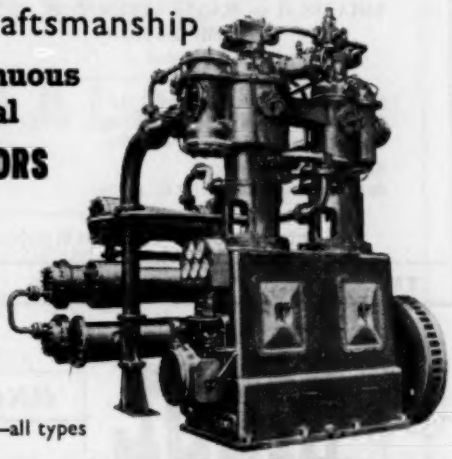

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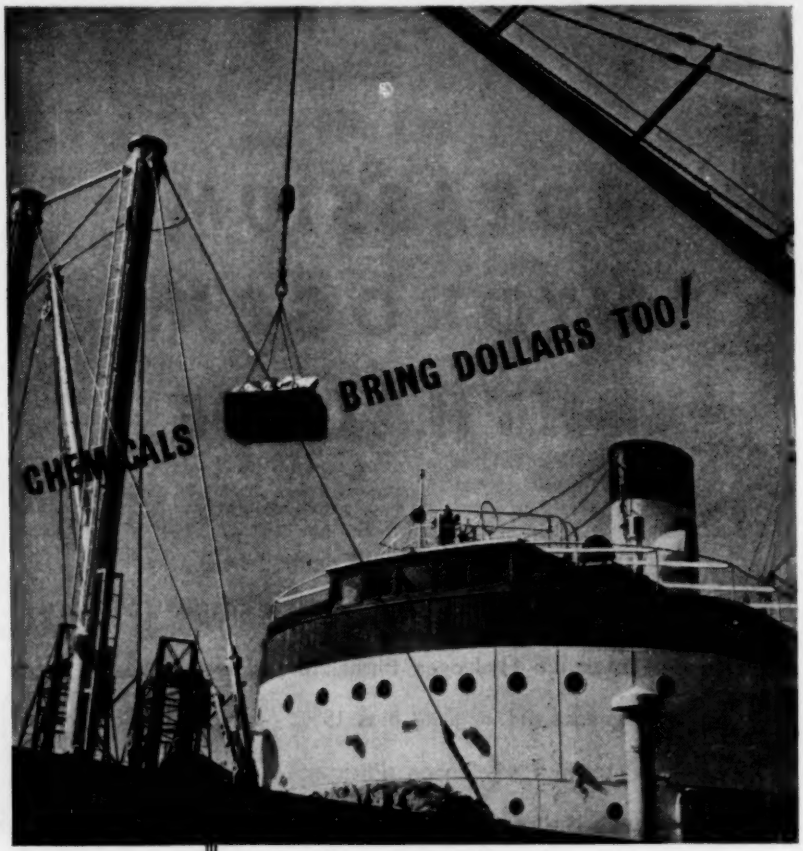

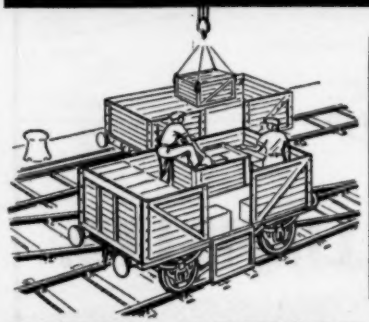

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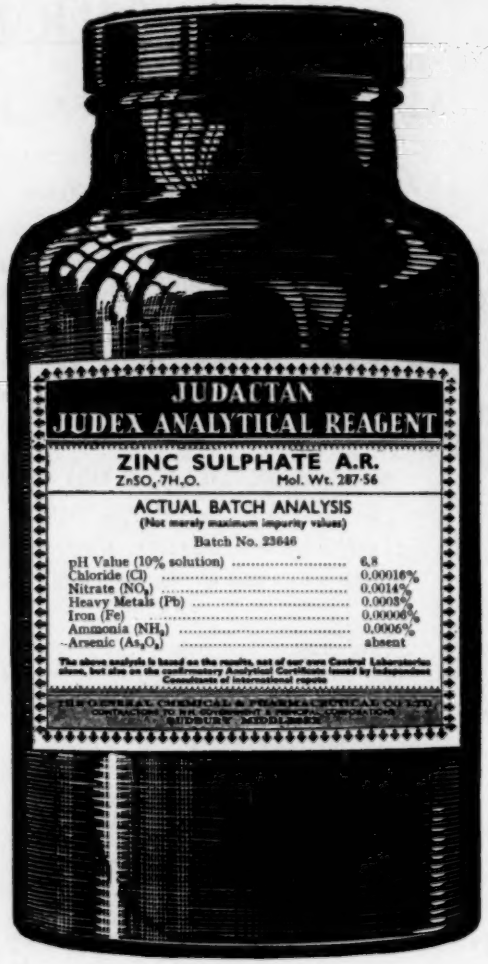
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SUMMARY. 9. Every paper must be prefaced by a short summary (50—250 words) setting forth briefly and in simple language the objects of the investigation and the results obtained. The summary should give any chemist a clear idea of what the investigation has achieved and should be independent of the main text. "Notes" do not require a summary.

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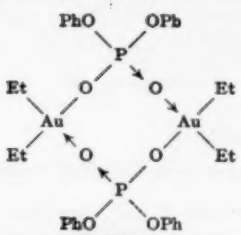
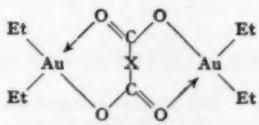
Interaction of the sulphato-complexes in aqueous solution with salts of dicarboxylic acids led to the isolation of non-electrolytes of various molecular complexities. The oxalato- (XXV; X = nil) and the phthalato-compound (XXV; X = *o*-$C_6H_4<$) each contained two atoms of gold per molecule. To the complexes derived from malonic up to suberic acid, containing


(XXIV.)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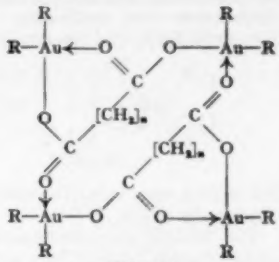
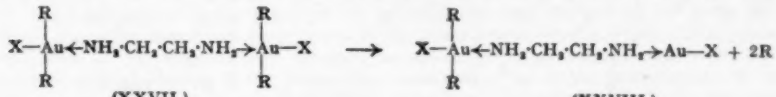

(XXVI.)

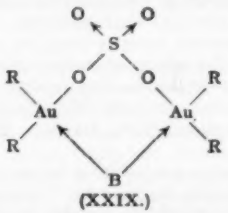
four atoms of gold per molecule, Gibson assigned provisionally the structure (XXVI; *n* = 1—6). The *iso*phthalate compound had no less than six gold atoms per molecule, whilst that derived from terephthalic acid was so insoluble that molecular-weight determinations were impossible, and extended linear polymerisation was postulated.

As had already been indicated, two molecular proportions of ethylenediamine convert dialkylgold halides into salts (XV; X = halogen). In the case of the cyanides no such salts could be isolated, the only products of the reaction being compounds, $(R_2AuCN)_2en$, in which it was believed that the diamine was " bridging " two R_2AuCN units, as in (XXVII; X = CN).


(XXVII.) (XXVIII.)

Gibson showed that under suitable conditions it was possible to prepare analogous compounds of dialkylgold halides and tetra-alkylsulphatodigolds (XXI), with ethylenediamine and di-2-pyridyl. Thus to the " bridged " sulphato-complexes the structure (XXIX; B = en or dipy) was given, their solubility in water to give sulphate ions being ascribed to the formation of aquo-salts (XXX), as in the case of the sulphato-complexes themselves.

The clue to the true constitution of these supposedly " bridged " compounds came as a result of a study of the dealkylation reactions which they underwent when heated. As early as 1935 Gibson recorded that ethylenediaminotetra-*n*-propyldibromodigold (XXVII; R = Pr^n,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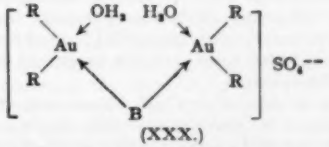

(XXX.)

X = Br as then formulated) lost only *half* its alkyl groups when heated in chloroform solution, to give a substance which he believed to be (XXVIII; R = Pr^n, X = Br). At the time no comment was made on the fact that whereas in the solid state dealkylation of (XXVII; R = Pr^n, X = Br) set in with uncontrollable vigour below 100°, (XXVIII; R = Pr^n, X = Br), though so closely related, lost its alkyl groups only at temperatures approaching 140°. Later in 1935 was published an account of the parallel reactions of monoethylenediaminotetraethyl- and tetra-*n*-propyl-dicyanodigold [believed to be (XXVII; X = CN, R = Et or Pr^n)], the products of the semidealkylation of which were recognised to be salts and correctly formulated

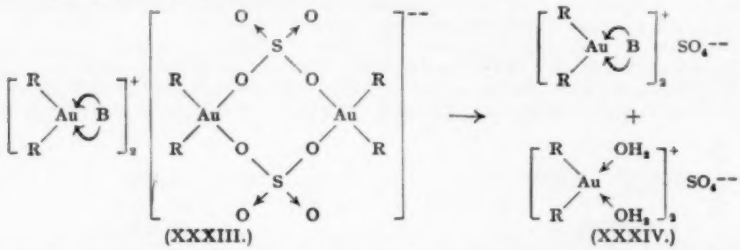
as aurocyanides (XXXII; X = CN, R = Et or Pr^n, B = en). These so similar reactions were, however, not correlated at the time.

Further investigation of ethylenediamine- and dipyridyl-bridged halides and cyanides, not only of type (XXVIII) but also of type (XXVII), showed that in dilute solution in nitrobenzene their molecular weights approached half their formula weights and that their solutions in nitrobenzene were conducting. These were hence re-formulated as (XXXI) and (XXXII) B = en or dipy), and the semidealkylation reaction was represented by :

(XXXI.) (XXXII.)

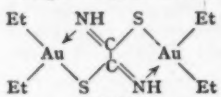
This is thus seen to be the entire loss of alkyl groups from the *anion only*, the cation being known to be stable.

The bridged ethylenediamine and di-2-pyridyl compounds (XXIX) of the tetra-alkyl-sulphatodigolds behaved in a similar manner but, in re-formulating them as (XXXIII), it was necessary to postulate the presence of a dimeric anion since the salts in solution were found to give rise to three ions. The effect on them of dissolution in water, as a result of which sulphate ion is disengaged, is hence represented by :



(XXXIII.) (XXXIV.)

As a result of these investigations much information accumulated regarding the stability of heterocyclic ring systems containing gold, and to augment this still further the reactions of diethylmonobromogold with 2-aminoethanethiol and dithio-oxamide were studied. Whilst the latter yields a stable complex (XXXV), the complex (XXXVI) derived from the former, though stable in the solid state, underwent in benzene and bromoform solution a rapid change which was attributed, at least in part, to inherent instability of the five-membered ring. The stability of (XXXV) was ascribed to resonance in the five-membered rings. The compound (XXXVI) gave also a sulphilimine (XXXVII) and reacted with ethyl bromide to give an oil for which, in spite of its physical characteristics, the ionic structure (XXVIII) was most favoured since it could be converted into a picrate (XXXIX), identical with that obtained by the action of sodium picrate on a solution containing diethylmonobromgold and 2-aminoethyl sulphide. The possibility of an alternative non-ionic structure (XL), or an equilibrium mixture of this and (XXXVIII), similar to that suggested to explain the properties of the *NN*-diethylenediamine complex (XLI), was thought less likely.

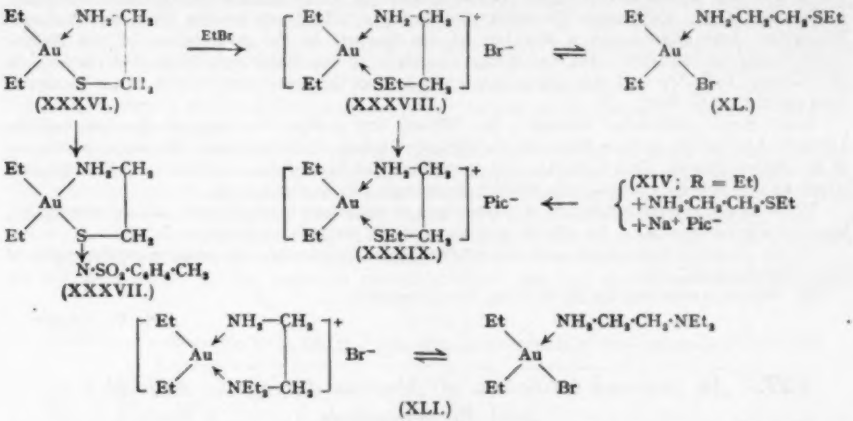


(XXXV.)

Every investigation which Gibson undertook in this field produced more evidence for the correctness of his main beliefs—that simple aurous and auric ions, Au^+ and Au^{+++}, cannot exist and that the gold atom, in either state of oxidation, must for stability acquire an additional covalent link, univalent gold thus becoming two-, and tervalent gold four-, covalent, and in the present account an attempt has been made to illustrate the diversity of the structural types which result.

No account of Gibson's work on gold would be complete without reference to his much prized process for the deposition of thin gold films on glass and other surfaces. The origin of the discovery is uncertain but it would have been surprising if, sooner or later, the action of alkali on an alcoholic solution of the dialkylgold halides had not been examined, though the resulting bright coherent " gold mirrors " which deposited on the walls of the vessels must have

astounded all who beheld them. Gibson spent several years of painstaking investigation in perfecting the process which in its final form consisted in exposing the surface to be gilded, after scrupulous cleaning, to a solution of diethylmonobromogold, calculated in amount to give the required film thickness, and sodium ethoxide in pure ethanol. Not only was it possible in this way to produce bright reflecting mirrors, which Gibson took great delight in presenting



to his friends, but also uniform transparent films so thin as to appear blue in transmitted light. The films were easily detached by rubbing and were floated off by water but, by a simple procedure discovered later, it was found possible to cover them with a thin protective layer of silica. So treated, they required no special care in handling and could even be submitted without damage to the lamination process employed in the manufacture of " safety glass." It is indeed unfortunate that Gibson never lived to bring his process to that state of commerical development upon which he had set such high hopes.

In the preparation of this notice I have been greatly assisted by Dr. M. P. Applebey, Dr. F. H. Brain, and Professor J. Read, F.R.S. Dr. Brain prepared the section dealing with the organic compounds of gold and Professor Read that on Professor Gibson's stereochemical investigations.

J. L. Simonsen.

DONALD CUMMING WILSON.

1898—1950.

The untimely death of Donald Cumming Wilson on 4th September, 1950, while on holiday at Boat of Garten, Inverness-shire, has all too soon removed from a unique sphere of influence one of Edinburgh's best known personalities in the chemical profession.

" D. C.," as he was affectionately called by his friends, was born in Tranent, East Lothian, on 3rd January, 1898, and received his early schooling at the local Higher Grade School and later proceeded to Broughton Secondary School, Edinburgh. He entered the Heriot–Watt College in 1915 and studied under the late Professor A. A. Boon, completing his course for the College Associateship in Applied Chemistry and simultaneously graduating B.Sc. (Edin.) in 1919. He was elected a Fellow of the Royal Institute of Chemistry in 1944 and a Fellow of the Royal Society of Edinburgh in 1945.

On leaving the College he joined the staff of Messrs. T. & H. Smith as a Works Chemist, being chiefly concerned with the Opiates Department. He won steady promotion in the firm and in 1941 he became a Director and in 1946 he was appointed Managing Director.

Mr. Wilson took a keen interest in foreign trade connected with pharmaceutical raw materials and products. In recent years he had visited the U.S.A., Canada, India, Sweden, France, and Denmark in pursuance of his Company's interests in such matters. Immediately before his

death, he attended at Geneva as trade representative for Britain on the Commission on Narcotic Drugs held under the auspices of the Economic and Social Council of the United Nations Organisation.

Mr. Wilson's health was not always of the best, but at no time did he spare himself in the service of his firm or in connection with matters of public interest in which he engaged. He was a Governor of the Heriot–Watt College, a Director of the Edinburgh Merchant Company, a Member of the Edinburgh Chamber of Commerce, Chairman of the Scottish Wholesale Druggists' Association, and a Member of the Council of the Association of the British Pharmaceutical Industry. He was a Past-Chairman of the Edinburgh Section of the Society of Chemical Industry and was one of the forces behind the foundation of the Lister Memorial Lecture of that Society.

Apart from professional interests, Mr. Wilson was a Past-President of the Corstorphine Literary Association and an Elder in St. Ninian's Church, Corstorphine. He was a keen lover of his native county, East Lothian, and spent many of his holidays in the Scottish Highlands where he was able to indulge in his hobbies of photography and motoring.

Mr. Wilson endeared himself to all with whom he came into contact by his absolute integrity, his constant consideration for others, and his sense of justice and fairplay.

To the chemical and pharmaceutical professions in Edinburgh, his passing, in the prime of life, is indeed a sad loss.

Mr. Wilson is survived by his wife and two daughters.

H. B. Nisbet.

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137. *An Induced Oxidation of Alcohols during the Reduction of Acid Permanganate.*

By J. H. Merz, G. Stafford, and William A. Waters.

During the action upon hydrogen peroxide or ferrous sulphate by acid permanganate primary and secondary alcohols can be oxidised immediately. If the alcohols are present in very large excess then *two* electrons of the five required for the valency change $(MnO_4)^- \longrightarrow Mn^{3+}$ can be derived from the alcohols, so that the induced oxidation is a non-chain process involving intermediate valency states of manganese. Additions of manganous or of pyrophosphate ions can check the oxidations of the alcohols, whilst addition of fluoride ions makes it more evident.

Since the presence of either the hydroxyl (·OH) or the 2-hydroxy-2-propyl ($Me_2\dot{C}$–OH) free radical would bring about the chain oxidation of *iso*propyl alcohol by hydrogen peroxide, which does not occur in these circumstances, neither of these free radicals can be concerned in the induced oxidation of *iso*propyl alcohol. It is suggested that the alcohols are oxidised by the transient Mn^{4+} ion in a two-electron change for which a mechanism is tentatively formulated. The Mn^{3+} ion is probably an intermediate involved in the oxidation of the hydrogen peroxide or of the ferrous salt.

The recent study of Fenton's reaction for the oxidation of alcohols by hydrogen peroxide (Merz and Waters, *Faraday Soc. Discussions*, 1947, **2**, 179; *J.*, 1949, S 15; 1949, 2427) has shown that during the reduction of hydrogen peroxide by ferrous ions there is produced a transient intermediate—the hydroxyl radical, ·OH—which is capable of oxidising organic substances that are not attacked by hydrogen peroxide molecules. In 1949 one of us (J. H. M.) made a brief preliminary survey of other reductions of hydrogen peroxide in order to ascertain whether it regularly occurred in two consecutive stages, *i.e.*,

$$HO\text{–}OH \xrightarrow{+1\varepsilon} \{(HO\cdot)^- + \cdot OH\} \xrightarrow{+1\varepsilon} 2(HO\cdot)^-$$

and found detectable induced oxidations of alcohols, due to hydroxyl radicals, only when one-electron donors, such as potassium ferrocyanide and cuprous chloride, which have oxidation–reduction potentials fairly close to that of the Fe^{3+}–Fe^{2+} system, were used. We now place these results on record.

In the course of this work, however, it was noticed that the mutual reduction of hydrogen

peroxide and potassium permanganate in the presence of sulphuric acid (1) was also a reaction during the course of which the simpler water-soluble primary and secondary alcohols could be oxidised rapidly. We have now examined this induced oxidation of alcohols in more detail and

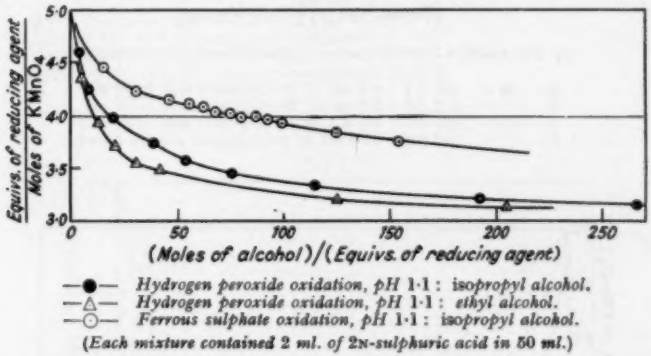
$$2(MnO_4)^- + 5H_2O_2 + 6H^+ \longrightarrow 2Mn^{2+} + 5O_2 + 8H_2O \quad . \quad . \quad . \quad . \quad (1)$$

find that it cannot be a reaction involving the hydroxyl radical, but must be a different process which is related to some stages in the reduction of $(MnO_4)^-$ to Mn^{2+} because a similar induced oxidation of alcohols can take place during the reduction of permanganate by ferrous sulphate in dilute sulphuric acid. This latter observation was described in 1914 by Doroshevskii and Bardt (*J. Russ. Phys. Chem. Soc.*, **46**, 754), and a different computation of their results, which we have confirmed and extended, discloses a new feature of the suspected stages of the Mn^{7+} to Mn^{2+} valency change.

At room temperature, dilute aqueous solutions of alcohols (if aldehyde-free) are not immediately attacked by acid permanganate. However, if a primary or a secondary alcohol is added to either ferrous sulphate or hydrogen peroxide in dilute sulphuric acid solution and these latter are then titrated in the cold with dilute potassium permanganate solution, then the reduction of the permanganate proceeds rapidly until a sharp, reproducible, end-point is reached. At this end-point *more* potassium permanganate has been consumed than the titre equivalent to the ferrous salt, or the hydrogen peroxide, alone, showing that some concurrent rapid

FIG. 1.

Oxidation of hydrogen peroxide, and of ferrous ions, by permanganate in the presence of an alcohol.



(*Each mixture contained* 2 *ml. of* 2N-*sulphuric acid in* 50 *ml.*)

oxidation of the alcohols has occurred. *tert.*-Butyl alcohol, acetone, and acetic acid were not detectably affected in this way.

Fig. 1 shows that if the titrations are plotted as

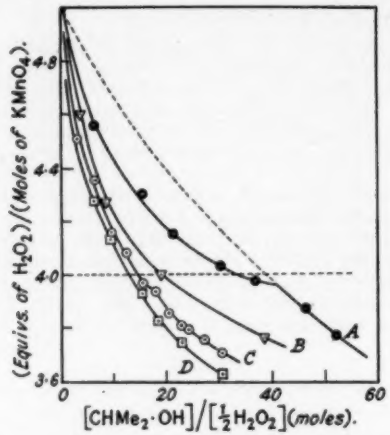
$$\frac{[\text{Equivs. of } Fe^{2+} \text{ (or } H_2O_2)]}{[\text{Moles of } KMnO_4]} \text{ against } \frac{[\text{Moles of alcohol}]}{[\text{Equivs. of } Fe^{2+} \text{ (or } H_2O_2)]}$$

then as the concentration of the alcohol in the solution is increased the first ratio progressively declines from 5 to 3. Hence, in the presence of a very large excess of a primary or secondary alcohol it appears that out of the five electrons acquired in oxidation by the Mn^{7+} it is possible to withdraw two, but no more, from an alcohol instead of from ferrous ions or molecules of hydrogen peroxide. Using methyl, ethyl, and *iso*propyl alcohols, we have found that, provided the reacting mixture is kept so strongly acid that no significant change of pH occurs, the end-points of these titrations are essentially independent of the overall dilution of the solution. Moreover, closely identical end-points can be reached by titrating hydrogen peroxide, or ferrous sulphate, into a mixture of an alcohol with dilute acid permanganate, though in these cases the appearance of a persistent pale yellow colour, probably due to a little colloidal manganese dioxide, make the procedure less accurate. This reversibility of the oxidation procedure shows conclusively that a chain reaction cannot be involved.

Though both primary and secondary alcohols exhibit the same type of induced oxidation in almost every detail, the precise character of the reaction can be followed most clearly by using

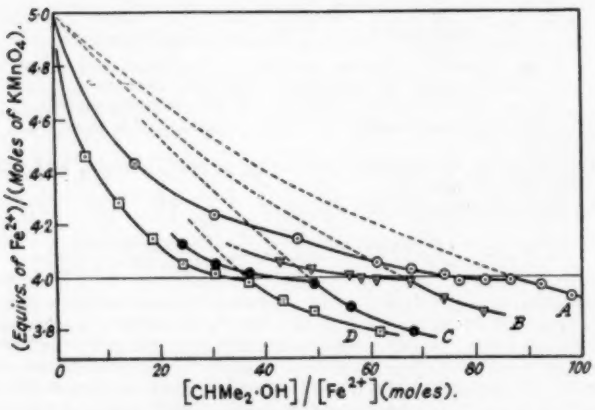
FIG. 2.

The effect of acidity of the extent of induced oxidation of isopropyl alcohol.



(*a*) *The reaction between hydrogen peroxide and permanganate:*

A. —●— *pH* 1·7: 0·5 *ml. of* 2N-*sulphuric acid in* 50 *ml.*
B. —▽— *pH* 1·1: 2·0 *ml. of* 2N-*sulphuric acid in* 50 *ml.*
C. —○— *pH* 0·7: 5·0 *ml. of* 2N-*sulphuric acid in* 50 *ml.*
D. —⊡— *pH* 0·4: 10·0 *ml. of* 2N-*sulphuric acid in* 50 *ml.*



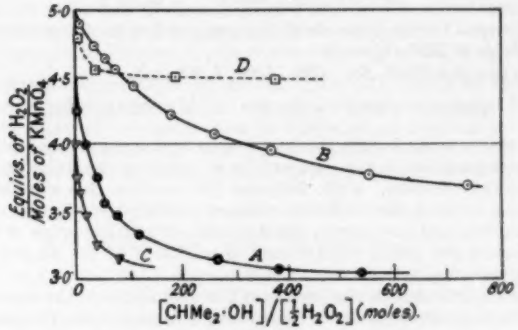
(*b*) *The reaction between ferrous sulphate and permanganate:*

A. —○— *pH* 1·1: 2·0 *ml. of* 2N-*sulphuric acid in* 45 *ml.*
B. —▽— *pH* 0·7: 5·0 *ml. of* 2N-*sulphuric acid in* 45 *ml.*
C. —●— *pH* 0·4: 10·0 *ml. of* 2N-*sulphuric acid in* 50 *ml.*
D. —⊡— *pH* 0·1: 20·0 *ml. of* 2N-*sulphuric acid in* 50 *ml.*

Each reacting mixture contained initially 20 *ml. of* 0·02N-*hydrogen peroxide in a total volume of* 50 *ml.*

FIG. 3.

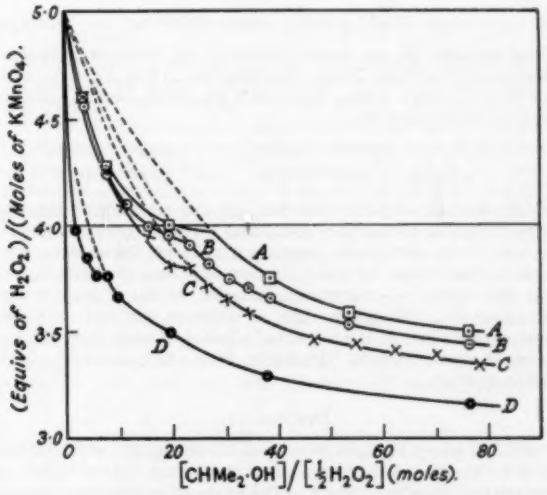
Effects of other ions on the induced oxidation of isopropyl alcohol by the hydrogen peroxide–permanganate reaction.



(*a*) *Effects of adding* Mn^{2+}, F^-, *and* $(P_2O_7)^{4-}$.

Each solution contains 2 ml. of 2N-*sulphuric acid in 50 ml. and :*

A. —●— (*No addition.*)
B. —○— 5 *Ml. of* 0·2M-*manganous sulphate.*
C. —▽— 5 *Ml. of* M-*sodium fluoride.*
D. —□— 10 *Ml. of* 0·1M-*sodium pyrophosphate* (*at* 60°).



(*b*) *The effect of adding fluoride anions.*

Each solution contains 2 ml. of 2N-*sulphuric acid in 50 ml. and :*

A. —□— *No added fluoride.*
B. —○— 0·02M-*Fluoride.*
C. —×— 0·10M-*Fluoride.*
D —●— 0·5M-*Fluoride.*

*iso*propyl alcohol as the substrate, because on oxidation it yields acetone which, under our conditions, is stable to any further oxidation. By varying the initial acidity of the sulphuric acid, the data plotted in Figs. 2(*a*) and 2(*b*) were obtained. These show (i) that the higher the acidity of the solution the greater is the initial ratio (Rate of oxidation of *iso*propyl alcohol)/(rate of oxidation of ferrous ion or of hydrogen peroxide), and (ii) that there is a slight, but definite, discontinuity in the ratio curves approximately corresponding to the oxidation ratio [Equivs. of Fe^{2+} (or H_2O_2)]/[Moles of $KMnO_4$] = 4.

Since Guyard's reaction (*Bull. Soc. chim.*, 1864, **1**, 89), *viz.*,

$$2(MnO_4)^- + 3Mn^{2+} + 4(OH)^- \longrightarrow 5MnO_2 + 2H_2O \quad . \quad . \quad . \quad . \quad . \quad (2)$$

is known to occur at low acidities, the results noted in (i) above indicate that one of the factors to be taken into consideration is the competition of electrons derivable from the manganous salt formed during the titration. Figs. 3(*a*) and (3*b*) confirm this surmise, since the initial addition of an excess of manganous sulphate reduces very significantly the extent of oxidation of the *iso*propyl alcohol, and conversely, the addition of a large excess of fluoride anions, to remove Mn^{3+}, enhances the initial relative rate of oxidation of the alcohol at low (*iso*propyl alcohol)/(hydrogen peroxide) ratios.

The addition of fluoride anions also enhances the magnitude of the discontinuity noted in (ii) above, but shifts its point of incidence towards an oxidation ratio, (Equivs. of H_2O_2)/(Moles of $KMnO_4$) = 3·8 to 3·85, *i.e.*, lower than 4. Extrapolation of the second portions of these discontinuous curves shows that two concurrent sets of competitive reactions may be involved.

It was also noticed that in the presence of fluoride ions the reduction of the permanganate became a much slower reaction. Launer and Yost (*J. Amer. Chem. Soc.*, 1934, **56**, 2571) have studied a similar retarding effect of fluorides in the reaction between acid permanganate and oxalic acid, Holluta (*Z. physikal. Chem.*, 1920, **101**, 34, 489) has observed it in the permanganate oxidation of formic acid, and Tomkins (*Trans. Faraday Soc.*, 1942, **38**, 131) has examined it in connection with the kinetics of the Guyard reaction (equation 2). These workers have ascribed the rate-retarding action of fluoride anions to the partial removal of manganous (Mn^{2+}) and manganic (Mn^{3+}) cations as insoluble salts, or as feebly dissociated complex ions, with the consequent disturbance of the rapid equilibrium (3), which, together with somewhat slower,

$$Mn^{2+} + Mn^{4+} \rightleftharpoons 2Mn^{3+} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

irreversible, changes such as (4) or, more probably, (5) (compare Bassett and Sanderson, *J.*, 1936, 207; Mann and Tompkins, *Trans. Faraday Soc.*, 1941, **37**, 201; Polissar, *J. Physical Chem.*, 1935, **39**, 1057; *J. Amer. Chem. Soc.*, 1936, **58**, 1372), are thought to be the principal components of the Guyard reaction (2).

$$2(MnO_4)^- + 3Mn^{2+} + 16H^+ \longrightarrow 5Mn^{4+} + 8H_2O \quad . \quad . \quad . \quad . \quad . \quad (4)$$

$$(MnO_4)^- + 4Mn^{2+} + 8H^+ \longrightarrow 5Mn^{3+} + 4H_2O \quad . \quad . \quad . \quad . \quad . \quad (5)$$

We have therefore studied also the influences on our reaction of phosphate and of pyrophosphate ions, since these also form stable complexes with manganese cations. Pyrophosphate ions, which form very stable manganic complexes, reduced the velocity of reduction of the permanganate so much that it was difficult to obtain definite end-points even at 60°, but it was clearly shown that the extent of concurrent oxidation of the *iso*propyl alcohol was greatly reduced [Fig. 3(*a*), curve *D*]. Phosphate ions, at different acidities, had comparatively little effect on the extent of oxidation of the *iso*propyl alcohol, though they did appreciably reduce the rate of reduction of permanganate. Probably their effect is chiefly due to their buffering action on the reacting systems.

Discussion.

Since primary and secondary alcohols do not react immediately with cold acid permanganate, their oxidation must be brought about by transient manganese ions of higher valency state than Mn^{2+} and of lower valency state than Mn^{7+}. The contrasting effects of adding manganous and fluoride ions show that, as in the permanganate–oxalic acid and permanganate–formic acid reactions, the reduction of the $(MnO_4)^-$ anion by the Mn^{2+} cation plays an important role in producing the manganese compound, or compounds, which actually do attack the organic molecules.

Now, in contrast to the earlier work with oxalic and formic acid, our present study of the induced oxidation of alcohols does furnish significant evidence concerning the valency state of

the active manganese compound which is involved, because it demonstrates that *it must be one*

$$CHMe_2\text{-}OH \xrightarrow{-1e} \dot{C}Me_2\text{-}OH + H^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

$$\dot{C}Me_2\text{-}OH \xrightarrow{-1e} Me_2C{=}O + H^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

that can undergo a two-electron valency change; for, if the oxidation of *iso*propyl alcohol by the reactive manganese compound involved a pair of successive one-electron changes (*e.g.*, 6 and 7), then, initially, the free 2-hydroxy-2-propyl radical, $\dot{C}Me_2$–OH, would be formed in a solution containing an excess of hydrogen peroxide (in the case of the permanganate–hydrogen peroxide reaction). Now our study of the mechanism of oxidation of alcohols by Fenton's reagent (Merz and Waters, *loc. cit.*) has proved that this free radical is able to decompose molecular hydrogen peroxide by the chain sequence (8) and (9) and to reduce mercuric ions to mercurous

$$\dot{C}Me_2\text{-}OH + HO\text{-}OH \longrightarrow Me_2C{=}O + \dot{O}H + H_2O \quad . \quad . \quad . \quad . \quad . \quad (8)$$

$$\dot{O}H + CHMe_2\text{-}OH \longrightarrow Me_2\dot{C}\text{-}OH + H\text{-}OH \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

ions. Hence it will be obvious that if the reaction between permanganate and an acid mixture of hydrogen peroxide and *iso*propyl alcohol did generate even traces of either the hydroxyl or the 2-hydroxy-2-propyl radical then the addition of a little potassium permanganate to the alcohol–hydrogen peroxide mixture should suffice to initiate the chain process (8) and (9). In that event the permanganate titre of the hydrogen peroxide would be greatly decreased by the presence of the alcohol, whereas, in fact, it is substantially increased. Again, it should have been possible to reduce mercuric salts during the reaction, and this definitely was not the case. Consequently, the oxidation of the alcohols must be brought about by manganese compounds only, and by a single step which can be represented as (10). Further, we can now exclude the

$$CHMe_2\text{-}OH - 2e \longrightarrow Me_2C{=}O + 2H^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

hypothesis that our only active intermediate in the $(MnO_4)^- \longrightarrow Mn^{3+}$ change is the manganic cation, Mn^{3+}, and can state that if this ion is formed then, under our conditions, it is not the entity which attacks the alcohols. This leaves a choice of the valency changes :

$$(a)\ (MnO_4)^{3-} \longrightarrow Mn^{4+};\ (b)\ Mn^{2+} \longrightarrow Mn^{3+};\ (c)\ Mn^{4+} \longrightarrow Mn^{3+}.$$

The active ion must have a sufficiently long free life to distribute itself uniformly through the reacting mixture, so as to be capable of acting competitively with both the alcohol and the main reducing agent (Fe^{2+} or H_2O_2). Consequently, transitions (*a*) and (*b*) are highly improbable, for there is never indication of even the transient production of the green manganate anion in acid media, whilst the valency state Mn^{5+} is unknown, even in complexes. The process (*c*), however, is a known valency change of manganese, though it has been represented as occurring in two successive one-electron stages (compare reaction 3). Again, there are many similarities between quadrivalent manganese and quadrivalent lead, and recent work (Rigby, *J.*, 1950, 1909; compare Criegee, *Annalen*, 1948, **560**, 132) indicates that lead, like bismuth, can acquire an inert pair of electrons by a single-stage process, $Pb^{4+} \longrightarrow (\dot{\dot{P}}b)^{2+}$.

The following sectionalised picture of a two-electron oxidation of an alcohol by the quadrivalent ion Mn^{4+} is an attractive hypothesis, which accords with the modes of action of active cationoid reagents, such as Br^+, $(OH)^+$, or $(H_3O_2)^+$ (Derbyshire and Waters, *Nature*, 1949, **164**, 446; 1950, **165**, 401), and nitrous acid (Clarke, Lapworth, and Wechsler, *J.*, 1908, **93**, 30; Woodward and Doering, *J. Amer. Chem. Soc.*, 1945, **67**, 866).

Stage 1. Co-ordination of the Mn^{4+} ion with the unshared electron pair of an oxygen atom :

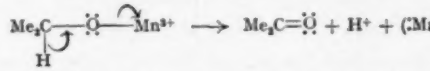
$$Me_2C(H)(H)\text{—}\ddot{O}: + (Mn)^{4+} \longrightarrow Me_2C(H)(H)\text{—}\overset{+}{O}\text{→}Mn^{3+}$$

Stage 2. (Immediate) Loss of proton from the oxonium cation to give an unstable mono-alkyl derivative of manganic hydroxide :

$$Me_2C(H)(H)\text{—}\overset{+}{O}\text{—}Mn^{3+} \longrightarrow Me_2C(H)\text{—}\ddot{O}\text{—}Mn^{3+} + H^+$$

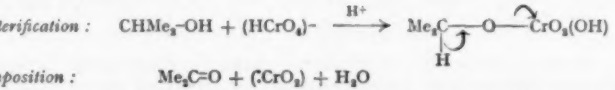
Stage 3. Transfer of the two covalency electrons of the manganic complex to the exclusive

control of the manganese nucleus, so as to form an inert pair, and the simultaneous release of proton from the C–H bond of the carbinol group:



Stage 1 may well be reversible, and probably is rate-determining, and stages 2 and 3 can be reagarded as electron drifts that set in immediately upon the completion of the co-ordinate link between the carbinol oxygen atom and the Mn^{4+} cation.

A similar mechanism can be postulated for the oxidation of *iso*propyl alcohol by aqueous chromic acid, where also a two-electron transition from Cr^{6+} to Cr^{4+} has been shown to occur (Westheimer and Nicolaides, *J. Amer. Chem. Soc.*, 1949, **71**, 25; Westheimer and Watanabe, *J. Chem. Physics*, 1949, **17**, 61) thus: *



The foreging hypothesis—that the oxidation of alcohols takes place at the $Mn^{4+} \longrightarrow Mn^{3+}$ valency change—accords with the view that the Guyard reaction proceeds by way of reactions (3) and (5) (p. 642). Of these, the rapid equilibrium (3) must be the more important in determining the relative concentrations of Mn^{4+} and Mn^{3+} ions present during the reduction of permanganate. Thus, a large excess of alcohol removes Mn^{4+} as soon as it is formed, but this cannot happen until something (Mn^{3+} or Fe^{2+}) has first reduced the permanganate to the Mn^{4+} level. The addition of manganous ions displaces the equilibrium (3) in favour of Mn^{3+}, and since this can react rapidly with Fe^{2+} (Bassett and Sanderson, *loc. cit.*), and probably with hydrogen peroxide too, the extent of oxidation of the alcohol is diminished. Fluoride ions, by partly removing both Mn^{3+} and Mn^{4+} cations, (i) displace equilibrium (3) in favour of Mn^{4+} and (ii) retard the oxidations depending upon Mn^{3+}. Pyrophosphate anions, by removing Mn^{3+} almost completely, both check the main oxidation depending upon Mn^{3+} and prevent the formation of Mn^{4+} and the consequent oxidation of the alcohol. The two-stage characters of the reaction curves of Figs. 2 and 3 are possibly to be accounted for in terms of the relative rates of formation of Mn^{3+} by the initial reduction of the permanganate anion (*e.g.*, by equation 5) and of its removal to form either Mn^{4+} or Mn^{3+}.

Experimental.

1. *Oxidation of Alcohols by the Reacting System Hydrogen Peroxide–Potassium Ferrocyanide* (J. H. M.).—The alcohol–ferrocyanide mixtures were oxidised at pH 1 with aproximately 0·1N-hydrogen peroxide, and after 12 hours the ferricyanide content of the solution was determined, following neutralisation, by reduction with potassium iodide in dilute acetic acid. Ferrocyanide anions were precipitated with an excess of M-zinc sulphate solution before titration of the liberated iodine with 0·02N-sodium thiosulphate (starch indicator). Each mixture contained, in 45 ml., 20 ml. of 0·1N-potassium ferrocyanide in 0·25N-sulphuric acid. Oxidation was effected with 10 ml. of approximately 0·1N-hydrogen peroxide.

Substrate: Ethyl alcohol.

$[EtOH]/[K_4Fe(CN)_6]$, mol.	0	20	50	100	150	200
$Na_2S_2O_3$ required, ml.	50	42·5	39·1	35·0	33·5	32·4
$[\Delta EtOH]/[\Delta K_4Fe(CN)_6]$	—	0·17	0·28	0·43	0·49	0·54

Substrate: iso*Propyl alcohol.* ...

$[CHMe_2{\cdot}OH]/[K_4Fe(CN)_6]$, mol.	0	0·5	1·0	1·5	2·5	4·0	6·0	10·0
$Na_2S_2O_3$ required, ml.	51	49·2	48·0	46·7	43·4	42·8	41·0	40·0
$[\Delta CHMe_2{\cdot}OH]/[\Delta K_4Fe(CN)_6]$	—	0·037	0·062	0·114	0·175	0·192	0·244	0·275

In alkaline solution potassium ferricyanide is reduced by hydrogen peroxide to ferrocyanide. The reaction was tested in solutions made 0·1N. with respect to potassium hydroxide. During the reduction of the ferricyanide and the conversion of the hydrogen peroxide into oxygen no concurrent oxidations of alcohols could be detected. The substrates used were ethyl and *iso*propyl alcohols, ethylene glycol, and glycollic acid.

* One of us (W. A. W.) is indebted to Professor F. H. Westheimer for helpful discussion of this mechanism.

2. *Oxidation of Alcohols by the Reacting System Hydrogen Peroxide–Sodium Cuprochloride,* Na_2CuCl_3 (J. H. M.).—The cuprochloride was made by dissolving freshly prepared cuprous chloride in 20% sodium chloride solution. The reaction is almost instantaneous, and the cupric ions were determined iodometrically without delay. Each mixture contained, in 30 ml., 10 ml. of 0·198N-cuprous chloride and 4 ml. of N-hydrochloric acid. 10 Ml. of 0·017N-hydrogen peroxide were added for each oxidation.

Substrate : Ethyl alcohol.

[EtOH]/[Cu^+], mol.	0·5	1·0	1·75	3·75	7·50	12·5	25·0	50·0
$Na_2S_2O_3$ reqd., ml.	52·2	51·3	50·5	48·6	44·7	43·5	38·8	35·7
[ΔEtOH]/[ΔCu^{2+}]	0·025	0·043	0·059	0·10	0·19	0·23	0·38	0·50

*Substrate : iso**Propyl alcohol.*

[$CHMe_2$·OH]/[Cu^+], mol.	1	2·5	4·0	6·0	8·5	12·5	20·0
$Na_2S_2O_3$ reqd., ml.	43·3	41·1	40·0	38·8	37·8	36·4	35·9
[$\Delta CHMe_2$·OH]/[ΔCu^{2+}]	0·039	0·095	0·125	0·160	0·190	0·236	0·254

3. *Oxidation of Alcohols by the Reacting System Hydrogen Peroxide–Acid Permanganate.*—0·02N-Potassium permanganate was titrated, at room temperature, into hydrogen peroxide–alcohol mixtures, each of which had a constant initial volume and contained identical amounts of hydrogen peroxide and sulphuric acid. The figures given below were reproducible irrespective of the rate of titration or of the degree of agitation of the mixture. The reversibility of the process was checked by taking the alcohol–permanganate mixtures corresponding to experiments marked * and then titrating them by 0·02N-hydrogen peroxide : in each case the same volume (±0·3 ml.) was required to decolorise the permanganate. The following results are typical of those plotted in Figs. 1 and 2.

Substrates : Methyl alcohol and ethyl alcohol.

Before titration each mixture (50 ml.) contained 20 ml. of 1·075 × 0·02N-hydrogen peroxide and 5 ml. of 2N-sulphuric acid.

[Moles of MeOH]/[Equivs. of H_2O_2]	0 *	29	58 *	174	290 *	579 *	1158 *	1450
$KMnO_4$ titre, ml.	21·5	23·5	24·75	27·50	29·40	31·50	33·45	34·10
[Equivs. of H_2O_2]/[Moles of $KMnO_4$]	5	4·57	4·35	3·90	3·66	3·41	3·21	3·15

[Moles of EtOH]/[Equivs. of H_2O_2]	4·13 *	12·4	20·6 *	31·0	41·4 *	124	206·5 *
$KMnO_4$ titre, ml.	24·60	27·10	28·80	30·10	30·70	33·40	34·10
[Equivs. of H_2O_2]/[Moles of $KMnO_4$]	4·35	3·95	3·71	3·55	3·48	3·20	3·13

Under comparable conditions the relative *initial* rates of oxidation of the substrates tested were : Methyl alcohol, 1·0; ethyl alcohol, 12·5; ethylene glycol, 2·8; *iso*propyl alcohol, 8·0; *sec.*-butyl alcohol, 8·7. *tert.*-Butyl alcohol and acetone were not attacked. At room temperature oxalic acid appeared to inhibit the reaction between potassium permanganate and hydrogen peroxide. Malonic acid had no immediate effect on the permanganate–hydrogen peroxide titre, but was oxidised fairly quickly by the resultant permanganate–manganese sulphate mixture.

The data plotted in Figs. 2(*a*) and 3 were obtained from similar experiments using *iso*propyl alcohol as the oxidisable substrate. The same total volume before titration (50 ml.) and the same quantity of hydrogen peroxide were used throughout, but the amount of acid, or of other component, was varied as indicated in each figure. It was found, however, that dilution of a prepared mixture with distilled water had no significant effect on the end-point of the titration. Nickel sulphate and mercuric nitrate were both found to be substances which could be added without effect on the titre. Consequently, there is no oxidation of Ni^{2+} comparable to that of Mn^{2+}, and no reduction of Hg^{2+} that would be indicative of the transient formation of an organic free radical, such as $\dot{C}Me_2$–OH.

The reactions conducted in the presence of fluoride and phosphate ions were slow, and the solutions needed warming. The data with the pyrophosphate, plotted in Fig. 3(*a*), were obtained at 60°. The curves obtained from reactions in which the phosphate ions, $(H_2PO_4)^-$ and $(HPO_4)^=$, were present did not differ significantly enough from those obtained in weakly acid solutions [Fig. 2(*b*)] to justify separate plotting, particularly since the sluggishness of the reaction made the experimental errors appreciable.

4. *Oxidation of Alcohols by the Reacting System Acid Permanganate–Ferrous Ion.*—A series of experiments, typical runs of which have been plotted of Fig. 2(*b*), corresponding to those of the previous section were carried out by using 0·02N-ferrous ammonium sulphate solution in place of hydrogen peroxide. On account of the possibility of precipitation of complexes of either Fe^{2+} or Fe^{3+} this study could not be extended to an investigation of the reaction in the presence of fluorides or phosphates. The reversibility of this reaction was also checked by titrating ferrous ammonium sulphate solution into prepared acid permanganate–*iso*propyl alcohol mixtures.

It should be noted that the initial ratio [Rate of oxidation of alcohol]/[rate of oxidation of main reducer] is much less when ferrous sulphate is used for reduction than when hydrogen peroxide is used.

We thank Dr. E. J. Bowen, F.R.S., for granting facilities for one of us (G. S.) to participate in this work.

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138. Acacia mollissima *Willd. Part I. The Component Sugars and Aldobiuronic Acid of Black Wattle Gum.*

By Alistair M. Stephen.

Black wattle gum differs from gum arabic in the proportions of sugars and uronic acid produced on acid hydrolysis. L-Arabinose (6), L-rhamnose (1), D-galactose (5), and D-glucuronic acid (1) have been shown to be combined in the approximate molecular ratios indicated. The equivalent weight (*ca.* 1880) is nearly double that of gum arabic. The aldobiuronic acid constituent, 6-(D-glucuronosido)-D-galactose, is the same as that present in gum arabic, egg-plum gum, almond-tree gum, and peach gum.

Black wattle gum is an exudate from the bark of *Acacia mollissima* Willd., produced on injury, or pathologically as a result of "gummosis." Unlike gum arabic, a product of various *Acacia* species, this complex acidic polysaccharide has not hitherto been investigated in detail or put to commercial use. The approximate molar proportions of the monosaccharide residues in gum arabic are L-arabinose (3), D-galactose (2), L-rhamnose (1), and D-glucuronosido-D-galactose (1), giving an equivalent weight of 1000—1200 (Butler and Cretcher, *J. Amer. Chem. Soc.*, 1929, **51**, 1519; Mukherji and Ghosh, *J. Indian Chem. Soc.*, 1949, **26**, 277). This composition may vary, because in certain samples no rhamnose has been detected (see Pigman and Goepp, "Carbohydrate Chemistry," 1948, p. 633). Removal of arabinose, rhamnose, and 3-L-arabinose-D-galactoside by mild hydrolysis leaves a degraded polysaccharide containing a basic repeating chain of six galactose residues, to numbers 1, 3, and 5 of which are linked terminal aldobiuronic acid groups. The structure of undegraded gum arabic is exceedingly complex; sugars other than galactose may constitute the main chains, and the glucuronic acid residues may not necessarily be present exclusively as end-groups (Smith, *J.*, 1939, 744, 1724; 1940, 1035; Jackson and Smith, *J.*, 1940, 74, 79). It is of interest that commercial sources of gum arabic are invariably trees located in hot dry climates (Pigman and Goepp, *op. cit.*).

Three samples of purified gum, prepared from fresh exudate by dissolution in weak alkali, acidification, and precipitation with ethanol, were similar in physical properties, thus indicating the raw material to be essentially homogeneous. The equivalent weight (*ca.* 1900) is considerably higher than that recorded for gum arabic. The number-average molecular weight of black wattle gum, determined by Mr. F. J. Joubert of this laboratory, is of the order of 92,000, decreasing slowly on account of hydrolysis. During the determination fragments are split off which are small enough to pass through a membrane capable of retaining particles of molecular weight *ca.* 30,000. Acid hydrolysis readily removes L-arabinose and smaller amounts of L-rhamnose and D-galactose (detected on one- and two-dimensional chromatograms), leaving a polysaccharide consisting predominantly of galactose and glucuronic acid residues in the proportion 5 : 1. The course of hydrolysis resembles that of the other plant gums, indicating that pentose units are present in the furanose form and hexose units in the pyranose form. More concentrated acid splits off four galactose residues per equivalent of polysaccharide, an aldobiuronic acid remaining which is resistant to dilute sulphuric acid at the ordinary pressure. Methylation of this acid, followed by hydrolysis, yields 2 : 3 : 4-trimethyl galactose and 2 : 3 : 4-trimethyl D-glucuronic acid, proving the aldobiuronic acid to be 6-(D-glucuronosido)-D-galactose. It is thus established that the components of black wattle gum are similar to those of gum arabic but are combined in different proportions. The polysaccharide remaining after removal of pentose and methylpentose, for example, can be represented in the same way as that obtained from gum arabic (Jackson and Smith, *locc. cit.*) except that in black wattle gum every fourth and not every second galactose residue in the repeating chain is linked to a 6-(D-glucuronosido)-D-galactose unit. In other words, the composition of degraded black wattle gum is the same as that of degraded gum arabic with every second aldobiuronic acid unit omitted.

The proportions of the components of black wattle gum have been determined (i) by complete hydrolysis of the gum with sulphuric acid and estimation of the resultant sugars by chromatographic separation and oxidation with periodate (Jones, *J.*, 1950, 534; Hirst and Jones, *J.*, 1949, 1659), and (ii) by partial hydrolysis of the gum to equal weights of the degraded acid polysaccharide (as its barium salt) and a mixture of sugars, followed by independent examination of the two fractions. The sugar mixture was shown to contain L-arabinose and L-rhamnose (cf. Hough, Jones, and Wadman, *J.*, 1949, 2511) by isolation of the pure sugars,

the ratios being determined by paper chromatography. In addition to employing the periodate oxidation method, roughly quantitative estimations were carried out by using the linear relation of spot area to the logarithm of sugar content of the spot (Fisher, Parson, and Morrison, *Nature*, 1948, **161**, 764). Instead of spraying ammoniacal silver nitrate the β-naphthylamine reagent recently evolved in this laboratory (Novellie, *ibid.*, in the press) was employed, the coloured spots being developed at 150° in order to obtain the clearest boundaries. The degraded polysaccharide mentioned above was further hydrolysed to an aldobiuronic acid and a mixture of sugars from which pure D-galactose was separated; the proportions of galactose, arabinose, and rhamnose in the residual syrup were then estimated by the means of spot areas.

Galactose, arabinose, and rhamnose have thus been shown to be in the molar ratio of 5·15 : 6 : 1 in the total hydrolysate of wattle gum, and this together with the known equivalent weight of the gum indicates a composition of D-galactose (5 parts), L-arabinose (6 parts), L-rhamnose (1 part), and D-glucuronic acid (1 part) with a calculated equivalent weight of 1940. As expected from a gum of this composition, the combined weights of arabinose and rhamnose are equal to that of the barium salt of degraded polysaccharide, and analysis of the mixed sugars has confirmed the arabinose : rhamnose ratio as 6 : 1. Both the barium content of the degraded polysaccharide salt and the weight of barium aldobiuronate recovered after removal of galactose are in agreement with a galactose : glucuronic acid ratio of 5 : 1.

Oxidation of the neutral gum with potassium periodate for two weeks (Brown, Dunstan, Halsall, Hirst, and Jones, *Nature*, 1945, **156**, 785) caused the production of very nearly two mols. of formic acid per equivalent of gum. If the acid is produced from $-[CH{\cdot}OH]_3-$ units only, this is consistent with the aldobiuronic acid residues being terminal as suggested above; each would be expected to liberate 2 mols. of formic acid on gentle oxidation. The network of galactose, arabinose, and rhamnose residues forming the main structure of the gum cannot possess this structural feature, indicating that either the D-galactopyranose residues are not linked in the 1 : 6 positions or, if they are so linked, they are engaged in glycosidic unions with pentose and methylpentose units.

Experimental.

The gum was collected from small trees in a native plantation in the Wartburg district of Natal (by courtesy of Mr. J. Hunt Holley). The trees were of varying ages and no attempt was made to discriminate between "wound" and "gummosis" gum. Collection took place during a two-week period in February towards the close of the heavy-rain season, when the gum was found as soft transparent jelly-like lumps which fermented on storage and dried to a horny mass during several months.

The crude gum was received as clear jelly-like lumps discoloured by reddish extracts from the bark. The bulk of it dissolved on gentle warming in sodium hydroxide solution, and purification was effected by repeated precipitation of the filtered, acidified solution in ethanol (see, *e.g.*, Brown, Hirst, and Jones, *J.*, 1948, 1677). The gum did not appreciably reduce Fehling's solution or form an insoluble copper derivative (see Deuel and Neukom, *Makromol. Chem.*, 1949, **4**, 97). It had $[\alpha]_D$ −49° in water. The iodine value, determined by Baker and Hulton's method (*Biochem. J.*, 1920, **14**, 754) was high and variable (5·6—11·5 c.c. of 0·1N-iodine per g. of gum after 20 minutes' oxidation) [Found: loss on vacuum desiccation at room temperature, 6·0; OMe, 0·35; ash, 1·2; pentosan, 48·5% (from Kröber's tables); equiv., 1880 (by titration with 0·01N-sodium hydroxide using methyl-red)]. The barium salt of the gum was prepared by addition of barium carbonate to an aqueous solution, filtration, and precipitation in ethanol (Found, on material dried at 100° *in vacuo*: Ba, 3·2. A polysaccharide of equiv. wt. 1880 requires Ba, 3·5%).

Quantitative Hydrolysis.—Dry purified black wattle gum (0·259 g.) was heated with 1·8N-sulphuric acid (10 c.c.) in a sealed tube in a boiling water-bath for 16 hours, and the cooled, partly neutralised (barium carbonate) hydrolysate poured through a column of Amberlite IR-4B anion-exchange resin. The neutral filtrate was then evaporated to small bulk (7·0 c.c.) under diminished pressure and analysed on an ascending paper partition chromatogram (cf. Partridge, *Nature*, 1946, **158**, 270; Flood, Hirst, and Jones, *J.*, 1948, 1679), with *n*-butanol–ethanol–water (4 : 1 : 5, upper layer). If the chromatogram was kept longer than 16—18 hours at 30° merging of the component sugars towards the solvent front, 18—23 cm. above the starting line, occurred. The positions of the different sugars on strips cut from the sheet were revealed by spraying the strips with Novellie's β-naphthylamine reagent and development at 140—150°. R_F values varied from one chromatogram to the next but the relative separation of the sugars was practically constant: rhamnose 0·63 (yellow), arabinose 0·43 (rose-pink), and galactose 0·33 (ochre). The individual sugars were extracted from the main sheet by cutting out appropriate strips, subdividing these into pieces no longer than 20 × 5 mm., and eluting them with three changes of warm water. Use of a Soxhlet device was unnecessary. Estimation of the sugars according to Hirst and Jones (*loc. cit.*) indicated the molar proportions of galactose, arabinose, and rhamnose in black wattle gum hydrolysate to be 5·15 : 6 : 1 (average of four determinations).

Graded Hydrolyses.—(a) *Autohydrolysis.* The changes in iodine value (expressed as c.c of 0·1N-iodine per g. of gum) on heating of black wattle gum (purified material, 12 g.) in water (100 c.c.) were as follows: 5·5 (initial value), 49 (17 hours), 61 (41 hours), 71 (65 hours). The polysaccharide recovered

by pouring the cooled, concentrated solution into ethanol had an increased iodine value (22) and retained moisture after vacuum-desiccation at room temperature (loss on drying at 100° *in vacuo*, 5·9%). During the hydrolysis samples were withdrawn and diluted to 2% concentration, and known volumes (0·01—0·02 ml.) placed on the starting line of an ascending chromatogram together with solutions of arabinose, rhamnose, and galactose of known strength. From the areas of the spots produced after the chromatogram (aqueous phenol at 31°) had run for 40 hours and then been sprayed with the β-naphthylamine reagent, the weights (in g.) of sugars produced from 1 g. of gum were calculated as follows: arabinose 0·25, rhamnose hydrate 0·03 (17 hours); arabinose 0·31, rhamnose hydrate 0·05 (41 hours); arabinose 0·335, rhamnose hydrate 0·06, galactose 0·025 (65 hours).

(b) *Hydrolysis with* 0·01N-*sulphuric acid.* The purified gum (7·5 g.) in 0·01N-sulphuric acid (250 c.c.) was heated on the boiling water-bath and the course of the reaction followed polarimetrically: $[\alpha]_D$ −47° (initial value); −10·7° (4 hours); +34·7° (21 hours); +36·7° (27 hours); +42·7° (43 hours). Previous experiment had shown the rate of change to be very slow during the last 10 hours. Iodine titration values were 69 (21 hours); 74 (27 and 43 hours). The neutralised (barium carbonate) reaction mixture was then filtered, evaporated to dryness at *ca.* 20 mm., and extracted with boiling methanol, giving a residue consisting of the barium salt of a degraded polysaccharide (3·33 g.; fraction A) and a syrupy mixture of sugars (3·765 g.; fraction B; containing *ca.* 0·20 g. of a barium salt) which crystallised partly when rubbed with cold methanol–acetone. Treatment of the mixed sugars (fraction B) with N-sulphuric acid (100 c.c.) on the water-bath for an hour caused no appreciable change in optical rotation ($[\alpha]_D$ +72°), indicating the absence of oligosaccharide. The recovered sugar mixture (3·56 g.) was then divided into a white solid powder (1·91 g., dried at 100°) and a viscous golden-brown syrup by trituration with methanol. The white solid contained a small proportion of barium (1·17%, corresponding to 7·2% of barium aldobiuronate) and had m. p. 143—145°, $[\alpha]_D^{18}$ +95·3° (*c*, 1·91 in water); examination on a paper chromatogram showed this to be mainly arabinose with a very faint galactose spot and a trace of barium salt at the origin. From this the arabinose content of the solid was estimated as 1·76 g. (92%). Recrystallisation of a portion of the solid from methanol and acetone yielded pure L-arabinose, m. p. and mixed m. p. 156°, $[\alpha]_D^{20}$ +105° (*c*, 0·785 in water). The benzoylhydrazone (see Hirst, Jones, and Woods, *J.*, 1947, 1048) had m. p. 195—199° (decomp.), raised to 206° by recrystallisation from ethanol; no depression when mixed with authentic L-arabinose benzoylhydrazone.

The syrup (1·65 g.; from fraction B) after removal of arabinose was examined on paper chromatograms in two ways. (i) 2% Solutions of the syrup in water (0·01 ml.) were run on an ascending chromatogram with known solutions of arabinose, galactose, and rhamnose hydrate, with aqueous phenol as solvent, and from the areas of the resulting spots the weights of the three sugars present were estimated as 0·92, 0·24, and 0·49 g., respectively. (ii) The syrup (3% solution; 0·1 ml.) was separated into its constituents and analysed by the periodate oxidation method of Hirst and Jones (*loc. cit.*); arabinose (0·83 g.), galactose (0·295 g.), and rhamnose hydrate (0·53 g.) were found and in addition a fourth component (faint pink spot with the β-naphthylamine reagent; R_F slightly lower than that of rhamnose) which was, however, insufficient in amount to estimate or identify. From the above results the weights of arabinose and rhamnose hydrate produced on mild hydrolysis of black wattle gum are in the ratio of 2·59 : 0·53 (molar ratio of 5·9 : 1).

Hydrolysed as before, the gum (90 g.) yielded a syrupy mixture of sugars from which crystalline L-arabinose (13 g.) was separated by trituration with methanol. A further crop crystallised after some weeks, and the residual syrup was then chromatographed on cellulose using water-saturated *n*-butanol (Hough, Jones, and Wadman, *loc. cit.*). Rhamnose hydrate, crystallising as long rectangular blades from the first eluate, had m. p. 98° and $[\alpha]_D^{20}$ +11° (*c*, 0·76 in water) after crystallisation from methanol–acetone. There was no m. p. depression on admixture with an authentic specimen of L-rhamnose hydrate, and the osazone had m. p. and mixed m. p. 180—181° (decomp.).

(c) *Examination of the degraded polysaccharide (fraction* A *above).* The polysaccharide salt remaining after removal of pentose and methylpentose by mild acid hydrolysis (fraction A) was dissolved in water, acidified with dilute sulphuric acid, and centrifuged to remove barium sulphate. The aqueous solution was then concentrated and poured into excess of ethanol kept at 5°, yielding a colourless flocculent polysaccharide which was dried in a vacuum (2·73 g.; loss on heating at 100° *in vacuo*, 9·0%). On evaporation of the bulk of the aqueous ethanol, treatment with barium carbonate and concentration of the filtrate a barium salt was recovered (0·40 g.) (Found: Ba, 9·0%) consisting of further hydrolysed material. The bulk of the degraded polysaccharide (2·68 g.) was made up to 100 c.c. with dilute sulphuric acid (2N.), and a portion (10 c.c.) of the solution reprecipitated in ethanol (100 c.c.) (Found, on material dried at 100° *in vacuo*: equiv., 930, by titration with 0·015N-sodium hydroxide using methyl-red; I absorption, 21·4 c.c. of 0·1N-iodine per g.).

The sulphuric acid treatment to remove barium had caused some hydrolysis, as results from a second experiment showed: in this case the barium salt of the polysaccharide, after thorough extraction of monosaccharides in boiling methanol, was dissolved in water and reprecipitated in ethanol [Found, on material dried at 100° *in vacuo*: Ba, 6·5; I absorption, 16 c.c. (as above). Calc. for polysaccharide salt containing 1 barium glucuronate and 5 galactose residues: Ba, 6·4%; equiv., 1004]. Hydrolysis of this substance in 0·1N-sulphuric acid at 96° for 9 hours caused a change in $[\alpha]_D$ from −13° to 0° (*c*, 1·84), and from the product a small quantity of galactose, arabinose, and rhamnose (in the approximate ratio of 3 : 3 : 1 from a paper chromatogram) and the barium salt of a polysaccharide (Found: Ba, 7·0%) were recovered.

The changes on hydrolysis of the polysaccharide (*c*, 2·68) in 2N-sulphuric acid on the boiling water-bath were as follows: $[\alpha]_D^{18}$ −12° (initial value), +6° (1 hour), +21° (4·5 hours), *ca.* +45° (6·5 hours); at this stage the solution was too dark to permit accurate measurement. I val. (as above): 53 c.c. (1 hour), 71 c.c. (2·5 hours), 79 c.c. (4·5 hours), 87 c.c. (6·5 hours), 89 c.c. (9 hours); the final titre corresponds to 0·80 g. of hexose in solution per g. of polysaccharide hydrolysed. Barium carbonate was added

in excess to the cooled solution, and after filtration the clear yellow liquid was evaporated under reduced pressure. The residue was extracted with boiling methanol (200 c.c.), leaving a yellow powder (0·78 g.; $[\alpha]_D$ 0°) which was strongly reducing (Found: Ba, 16·0; I absorption, 53 c.c. Calc. for $C_{12}H_{19}O_{12}Ba_{0·5}$: Ba, 16·2%; I absorption, 47 c.c., calculated from the known value for galactose). The yield on the weight of dry polysaccharide taken (43·8%) was in agreement with that (42·2%) expected from a polysaccharide containing one uronic acid and five hexose residues. No sugars were present, a paper chromatogram showing only a distinct spot at the origin.

The methanol extract, after evaporation to dryness and washing with a little cold methanol–acetone, yielded crystalline D-galactose (0·68 g.), m. p. 160—165° (foaming), $[\alpha]_D^{20}$ +98° ⟶ +77° in 4 hours, final value +74°, and a syrup (0·22 g.). A portion of the solid (0·228 g.) with methylphenylhydrazine in aqueous ethanol (Hirst, Jones, and Woods, *loc. cit.*) yielded a derivative (0·318 g.), m. p. and mixed m. p. 187—188° (decomp.), raised to 190° (decomp.) on recrystallisation from aqueous ethanol. A specimen of pure D-galactose gave a similar weight of the methylphenylhydrazone on treatment in the same way. A second sample of the solid yielded mucic acid, m. p. and mixed m. p. 220° (decomp.), on oxidation with nitric acid. The syrup, oxidised similarly, gave approx. 70% as much mucic acid, indicating that it contained 0·15 g. of galactose; a paper chromatogram revealed the presence of galactose with traces only of arabinose and rhamnose.

Identification of the Aldobiuronic Acid.—Black wattle gum (dry weight 25·0 g.; equiv. 1880) in 2N-sulphuric acid (75 c.c.) was hydrolysed for 6 hours and worked up in the usual way, to give a methanol-insoluble barium salt (4·35 g.; calc. yield of barium aldobiuronate, 5·6 g. Found: Ba, 15·9%). A portion (0·1 g.), after 3·5 hours' heating with 3N-sulphuric acid (1·5 c.c.) in a sealed tube immersed in a boiling water-bath, did not contain galacturonic acid residues according to Ehrlich's basic lead acetate test (*Ber.*, 1932, **65**, 352). The barium aldobiuronate (1·65 g.) was methylated and the resulting methyl heptamethylaldobiuronate {0·52 g.; b. p. *ca.* 220° (bath-temp.)/0·15 mm.; n_D^{18} 1·4664, $[\alpha]_D^{18}$ +28° (*c*, 1·32 in water)} characterised by hydrolysis with 1·5N-hydrochloric acid to give (i) 2 : 3 : 4-trimethyl galactose, n_D^{18} 1·4650, $[\alpha]_D$ +94° (*c*, 1·62 in water) (Found: OMe, 43·3. Calc. for $C_9H_{18}O_6$: 3OMe, 41·9%) [anilide, colourless needles, m. p. 163—165° after being washed with ethanol (lit., 168°, 169°)], and (ii) the ether-insoluble barium salt of an acid which on oxidation with bromine and esterification with methanolic hydrogen chloride afforded the methyl ester, m. p. 108—109° (distilled at 0·1 mm. and recrystallised from ethanol–*iso*hexane) (lit., m. p. 107°, 110°, 111°), of 2 : 3 : 4-trimethyl D-glucosaccharo-lactone. The aldobiuronic acid component of black wattle gum is thus identical with that of gum arabic (Smith, *J.*, 1939, 1724), egg-plum gum (Hirst and Jones, *ibid.*, 1947, 1064), almond-tree gum (Brown, Hirst, and Jones, *loc. cit.*) and peach gum (Jones, *loc. cit.*). Confirmation of the structure of the galactose derivative was obtained by oxidizing it with periodate, whereupon formaldehyde (dimedone compound, m. p. and mixed m. p. 188°) was evolved.

Periodate Oxidation of the Gum.—The purified gum (0·293 g.) was neutralised with 0·01N-sodium hydroxide, and after addition of sodium metaperiodate solution (20 c.c.; 0·2M.) and potassium chloride (2 g.), was made up to 50 c.c. in a standard flask. The stoppered flask was kept in the dark and shaken occasionally. At intervals portions (5 c.c.) were withdrawn and titrated with 0·01N-sodium hydroxide after addition of ethylene glycol (5 drops, excess) [Found: 2·85 c.c. (190 hours); 3·03 c.c. (330 hours); 3·68 c.c. (1 month). Methyl-red used as indicator]. These results correspond to the production of 1 g.-mol. of formic acid from 1030, 970, 800 g. of gum respectively, *i.e.*, 1·83, 1·93, and 2·35 mols. of acid from one equivalent of gum (1880).

The author thanks the South African Council for Scientific and Industrial Research for permission to publish this paper, and Professor F. L. Warren and Mr. L. Novellie for helpful discussion in connection with paper chromatography techniques.

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139. *The Orientation of* x-*Bromo- and* x-*Nitro-benzocinnoline 6-Oxides.**

By K. E. CALDERBANK and R. J. W. LE FÈVRE.

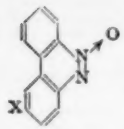
The dipole moments of the two compounds named in the title indicate that in both cases the substituent is in the 3-position. Benzocinnolines and their 6-oxides appear to be characterised by ultra-violet absorptions at *ca.* 3000 A. ($\log_{10}\varepsilon$ = 3·7—3·9) and 3300—3500 A. ($\log_{10}\varepsilon$ = 3·9—4·2), respectively.

FOLLOWING observations described before (Calderbank and Le Fèvre, *J.*, 1948, 1949) we have examined the products of monobromination and mononitration of benzocinnoline 6-oxide (I).

* In the paper and in papers discussed therein the Ring Index enumeration for benzocinnoline is used, and the nitrogen carrying the oxygen is numbered 6. Correctly it should be given the lower number possible, *i.e.*, 5.—ED.

Dielectric-polarisation and spectrographic data for these and related molecules are included in this communication.

(I.)



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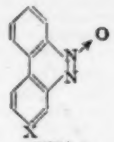

(III.)

Dipole-moment Measurements.—In our 1948 paper the moment of benzocinnoline 6-oxide (I) was reported as 5·2 D., while the corresponding datum for benzocinnoline was 3·9 D. Since the link moment of N → O seems to be about 1·7 D. (*i.e.*, the difference between the observed values for *trans*-azo- and -azoxy-benzenes, 0 and 1·7 D., respectively) we may consider the resultant in (I) to be disposed across the molecule in a direction between two and three o'clock and with its negative pole outwards. Provided that the axes 9 : 10 : 1 : 2 and 6 : 5 are approximately parallel and that no unexpected mesomeric polarisations occur, it is evident that—if X = Br or NO_2—(II) should be less polar than (III).

On the figures just quoted we calculate the resultant of (I) to lie 75—80° clockwise from the 5 → 6 line. Accordingly, if the vectors associated with bromo- and nitro-group are 1·6 and 4·0, the following moments are to be expected for 2- and 3-monosubstituted derivatives of (I):

	Substituent at position (2).	(3).
Bromobenzocinnoline 6-oxide	3·7 D.	5·0—5·2 D.
Nitrobenzocinnoline 6-oxide	1·7—1·0	5·7—6·0

From measurements tabulated later polarities are actually found as follow:

3 : 8-Dichlorobenzocinnoline 6-oxide ..... 5·1 D.

x-Bromobenzocinnoline 6-oxide ..... 5·3 *x*-Nitrobenzocinnoline 6-oxide ..... 5·6

The disubstituted oxide is included to test the assumption of colinearity of the "diphenyl" part of (I); if this is correct the moment of the 3 : 8-dichloro-compound should be very close to that (5·2 D.) of its parent. Agreement is, in fact, highly satisfactory.

On the argument used above, the mono-bromo- and -nitro-derivatives appear to be 3-isomers in each case. Such an inference is contrary to King and King's conclusions (*J.*, 1945, 824) where nitration is concerned. These authors found benzocinnoline 6-oxide to give, with fuming nitric acid, mainly that nitro-product, m. p. 269°, to which our measurements relate, together with smaller amounts of an isomer, m. p. 226°. By total reduction, followed by ring-closure, etc., aminocarbazoles, m. p. 243° and 240°, were isolated, recognised by their melting points as 3-aminocarbazole (Ullmann, *Annalen*, 1903, **332**, 101), and 2-aminocarbazole (Blank, *Ber.*, 1891, **24**, 306), respectively. Yet the m. p.s quoted in the literature (cf. Beilstein, "Handbuch," Vol. XXII, p. 460) are 238° for the 2-derivative, and 246—248°, or 254°, or 240—259° (decomp.) for the 3-derivative. It does not appear from King and King's paper that they determined mixed m. p.s or directly compared authentic specimens of the aminocarbazoles with their own end products. We suggest therefore that the orientations of the nitro-compounds, m. p. 269° and 226°, have not yet been rigidly demonstrated by chemical methods.*

Absorption Spectra.—These have been determined in M/20,000-ethyl alcoholic solution with the Beckman Photoelectric Quartz Spectrophotometer, Model D.U. The wave-lengths and extinctions ascribable to general conjugation between the $-N{=}N-$ systems and the associated

* The point has been discussed with Professor F. E. King and Dr. T. J. King who comment as follows. "The identification of the aminocarbazole derived from the principle nitration product, m. p. 269°, of benzocinnoline 6-oxide was based on the correspondence of the m. p. (218°) of its analytically pure *N*-acetyl compound and that of 3-acetamidocarbazole (217°) as determined by Ullmann (*loc. cit.*). Owing to the lack of concordance between the literature values for 3-aminocarbazole, less importance can be attached to the decomposition temperature (240°; 243°, after crystallisation) of the corresponding aminocarbazole (King and King, *loc. cit.*, where Ullmann's m. p. for 3-aminocarbazole is inexplicably misquoted), although it is higher than that of 2-aminocarbazole (238°). Nevertheless, in view of the dipole determination by Calderbank and Le Fèvre, our conclusions as to the orientation of the nitrocinnoline 6-oxides cannot be maintained."

Ar-nuclei [*K* bands on Braude's classification (*Ann. Reports*, **1945**, **42**, 105), cf. Cook, Jones, and Polya, *J.*, **1939**, 1315] are listed in the following table:

	$\lambda_{max.}$	$\log_{10}\varepsilon$.		$\lambda_{max.}$	$\log_{10}\varepsilon$.
Benzocinnoline	3000	3·87	Benzocinnoline oxide	3320	3·97
1 : 10-Dimethyl- ,, ...	2940	3·73	3 : 8-Dichloro- ,, ...	3320	3·86
3 : 8-Dichloro- ,, ...	3060	3·74	*x*-Nitro- ,, ...	3420	4·12
			x-Bromo- ,, ...	3440	4·01

The seven examples fall into two groups, the oxides absorbing at wave-lengths *ca.* 300 A. longer than the benzocinnolines, and with a slightly greater intensity. *cis*-Azo- and -azoxy-benzenes [$\lambda_{max.}$ ($\log_{10}\varepsilon$): 3050 (3·5) and 3350 (3·9), respectively] also fit this generalisation. The points made by Calderbank and Le Fèvre (*J.*, **1948**, 1949) therefore receive further support.

Experimental.

Benzocinnoline 6-oxide (m. p. 138°) and its mononitration product (m. p. 269°) were prepared as described by King and King (*loc. cit.*). 1 : 10-Dimethyl- and *x*-bromo-benzocinnoline 6-oxides were presented to us by Mr. P. H. Gore, M.Sc. (who will be describing the latter in a separate publication; the former, m. p. 153°, was first isolated by Sako, see below). The 3 : 8-*dichloro-oxide* was obtained by reducing 4 : 4′-dichloro-2 : 2′-dinitrodiphenyl (Ullmann and Bielecki, *Ber.*, **1901**, **34**, 2176) by Sako's sodium sulphide nonahydrate method (*Bull. Chem. Soc. Japan*, **1934**, **9**, 393); after recrystallisation from benzene and then alcohol it formed pale-yellow needles, m. p. 244—245° (Found: C, 54·1; H, 2·35; N, 10·5; Cl, 26·8. $C_{12}H_6ON_2Cl_2$ requires C, 54·4; H, 2·3; N, 10·6; Cl, 26·75%). Nitration by dissolution in absolute nitric acid on the water-bath followed by pouring on ice, etc., gave a cream-coloured powder, crystallisable from acetic acid, but sparingly soluble in other solvents. Analysis suggested that it was a *dinitro*-derivative, m. p. 294—295° (Found: N, 15·6. $C_{12}H_4O_5N_4Cl_2$ requires N, 15·8%). "Sako" reductions of 3 : 3′ : 5 : 5′-tetrachloro- and 3 : 3′ : 4 : 4′ : 5 : 5′-hexachloro-2 : 2′-dinitrodiphenyls (Roosmalen, *Rec. Trav. chim.*, **1934**, **53**, 359) yielded products with high m. p.s and little solubility in organic solvents.

3 : 8-*Dichloro-* and 1 : 10-*dimethyl-benzocinnolines* were obtained by reducing the corresponding oxides with the calculated quantities of stannous chloride in concentrated hydrochloric acid. They formed small, pale-yellow (m. p. 259—260°) and colourless (m. p. 135—136°) crystals from alcohol (Found: N, 11·15 and 13·3 respectively. $C_{12}H_6N_2Cl_2$ requires N, 11·25. $C_{14}H_{12}N_2$ requires N, 13·4%).

The measurements tabulated below were made at 25°, benzene being used as solvent. Symbols and procedures for calculation have been explained previously (Calderbank and Le Fèvre, *loc. cit.*, cf. also Le Fèvre, *Trans. Faraday Soc.*, **1950**, **46**, 1).

Measurements.

$100w_1$.	$\varepsilon_{25°}$.	d_4^{25}.	$\alpha\varepsilon_2$.	βd_2.	$100w_1$.	$\varepsilon_{25°}$.	d_4^{25}.	$\alpha\varepsilon_2$.	βd_2.
0	2·2725	0·87378	—	—	—	—	—	—	—
3 : 8-*Dichlorobenzocinnoline* 6-*oxide*.									
0·2017	2·2931	0·87450	10·21	0·257	0·4112	2·3125	0·87529	9·73	0·367
0·2613	2·3004	0·87470	10·68	0·352	0·5321	2·3225	—	9·40	—
0·2971	2·3016	0·87486	9·80	0·363					
Whence $(\alpha\varepsilon_2)_{w_1} = 10·99—301w_1$; $\Sigma(d_{12} - d_2)/\Sigma w_1 = 0·3611$.									
Nitrobenzocinnoline 6-*oxide* (*m. p.* 269°).									
0·1854	2·2979	0·87451	13·70	0·394	0·2645	0·3064	0·87494	12·74	0·439
0·2112	2·3000	0·87470	13·00	0·436	0·3012	2·3105	0·87492	12·62	0·379
Whence $(\alpha\varepsilon_2)_{w_1} = 15·02—837w_1$; $\Sigma(d_{12} - d_2)/\Sigma w_1 = 0·4105$.									
Bromobenzocinnoline 6-*oxide* (*m. p.* 194·5°).									
0·0695	2·2806	0·87396	11·65	0·259	0·2024	2·2952	0·87477	11·21	0·489
0·1595	2·2908	0·87437	11·47	0·370	0·3181	2·3085	0·87501	11·32	0·387
Whence $(\alpha\varepsilon_2)_{w_1} = 11·67—140w_1$; $\Sigma(d_{12} - d_2)/\Sigma w_1 = 0·3989$.									

Calculation of results.

Benzocinnoline 6-oxide.	M_1.	$(\alpha\varepsilon_2)_{w_1=0}$.	Mean β.	${}_mP_1$.	$[R_L]_D$.*	μ, D.
3 : 8-Dichloro-	265·0	$10·9_9$	$0·413_2$	600·8	75·9	$5·0_8$
x-Nitro-	241·1	$15·0_2$	$0·469_5$	724·7	72·5	$5·6_4$
x-Bromo-	275·0	$11·6_7$	$0·456_5$	654·6	74·0	$5·3_2$

* Taking $R_H = 1·10$, $R_{Cl} = 5·97$, $R_{NO_2} = 7·36$, $R_{Br} = 8·86$ in conjunction with the previously observed value of 66·2 c.c. for the unsubstituted oxide (Calderbank and Le Fèvre, *loc. cit.*)

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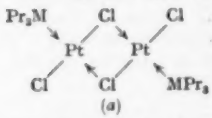
140. *The Nature of the Co-ordinate Link. Part II. Halogen-bridged, Binuclear Platinous Complexes. The Co-ordinating Affinity of the Tertiary Alkyls of Group V Elements for Platinous Chloride.*

By J. Chatt.

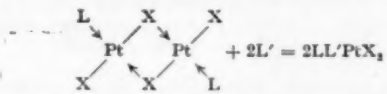
Halogen-bridged compounds of type (*a*) (M = P, As, and Sb) have been prepared. No evidence of geometric isomerism has been observed in this series of complexes, and only the *trans*-symmetrical forms were found. Neither simple nor bridged tri-*n*-propylamine complexes could be obtained, but the unsymmetrical *trans*-$[MPr_3,NPr_3,PtCl_2]$ (M = P and As) have been prepared. With *p*-toluidine the bridged complexes yielded the unsymmetrical *trans*-$[C_7H_7\cdot NH_2,MPr_3,PtCl_2]$ as in the reaction with the corresponding palladous bridged complexes, but with 2 : 2′-dipyridyl the salt $[MPr_3,dpy,PtCl]^+[Pr_3M,PtCl_3]^-$ was obtained (M = P and As only). The phosphine salt was stable, but the arsine salt decomposed in solution to $(AsPr_3)_2PtCl_2$ and dpy $PtCl_2$ at room temperature. The stibine bridged compound behaved as do the palladium compounds and produced $(SbPr_3)_2PtCl_2$ and dpy $PtCl_2$ immediately on reaction with dipyridyl. Attempts to prepare a bismuthine complex were unsuccessful.



(*a*)

On the basis of the observed stabilities of these compounds, the co-ordinating affinity of these ligands towards platinous chloride is considered to be in the order $PPr_3 > AsPr_3 > SbPr_3 > NPr_3 > BiPr_3$. It was shown by attempting to place ethylene in this series that the relative co-ordinating affinity of ligands is very sensitive to the nature of the ligands already attached to the metal.

We intend to measure the dipole moments of a number of unsymmetrical *trans*-compounds of the type $LL'PtX_2$ (L = neutral ligands; X = univalent acid radicals), to obtain a more quantitative measure of the part played by filled *d* orbitals in co-ordination to platinous salts (Chatt, *J.*, 1949, 3340; *Nature*, 1950, **165**, 637). The readiest synthesis of these complexes appears to lie through the bridged complexes according to the reaction :



Accordingly, a series of platinous halogen-bridged complexes of general formula $(MPr^n_3,PtX_2)_2$ (M = P, As or Sb) has been prepared and is now described in view of its interest.

Although one of the first binuclear complexes to be isolated, namely, $(COPtCl_2)_2$ (Schützenberger, *Bull. Soc. chim.*, 1870, **14**, 17), was a halogen-bridged platinum complex, the number of known platinous complexes of this class is surprisingly small, except for two or three organic sulphide derivatives and one selenide derivative, which are too insoluble in organic solvents for thorough chemical investigation (Jensen, *Z. anorg. Chem.*, 1935, **225**, 124); the few that are known cannot be considered typical. They contain unusual ligands, for example, CO, PCl_3, $P(OEt)_3$ (Schützenberger, *Bull. Soc. chim.*, 1872, **17**, 482; **18**, 148), C_2H_4 (Anderson, *J.*, 1934, 971), and PF_3 (Chatt, *Nature*, *loc. cit.*). The CO, PCl_3, and PF_3 complexes are decomposed at once by moisture and the bridged structure is assumed. The olefin co-ordination complexes are less sensitive to moisture, yet are not very stable or amenable to study. The bridged complexes of phosphorus trichloride and triethyl phosphite were investigated by Rosenheim and his co-workers (*Z. anorg. Chem.*, 1903, **37**, 394; 1905, **43**, 35), who showed that the complex $P(EtO)_3,PtCl_2$ is dimeric and studied its reaction with amines.

The halogen-bridged structure was put forward in 1923 by Pfeiffer ("Anorganischen Chemie," pp. 56, 170) but the existence of such a structure was not confirmed until it was shown by complete *X*-ray crystal-structure determination to exist in diethylmonobromogold $(Et_2AuBr)_2$(Burawoy, Gibson, Hampson, and Powell, *J.*, 1937, 1690), and in dibromobis(trimethylarsine)-$\mu\mu'$-dibromodipalladium $(AsMe_3,PdBr_2)_2$ and its chlorine analogue (Mann and

Wells, *J.*, 1938, 702; Wells, *Proc. Roy. Soc.*, 1938, *A*, **167**, 169). Since then, easily soluble tertiary phosphine and arsine halogen-bridged complexes containing many other metals, particularly from the second and the third long series of the Periodic Table, have been prepared and studied, yet platinous bridges have received no further study because no general synthetic method had been found.

Platinous bridged complexes are of especial interest. The simple platinous complexes, L_2PtX_2, are the most rigid of all planar complex compounds as shown by the existence of a large number of stable *cis*- and *trans*-isomers; hence, if geometric isomerism exists amongst bridged complexes, it is most probably to be found in the platinous series. Also, rearrangement of platinous complexes during reaction is less likely to occur than in any other planar complex compounds. Hence, it is interesting to compare their reactions with typical reactions in the similar palladium series, where there is lability of geometric isomers and rearrangements take place spontaneously (Mann, *Ann. Reports*, 1938, **35**, 150; Chatt and Mann, *J.*, 1939, 1622).

Preparation and Properties of Bridged Platinous Complexes of Tri-n-propyl-phosphine, -arsine, and -stibine.—The tertiary phosphine and arsine bridged complexes are most conveniently prepared by direct reaction of powdered platinous chloride with a crude mixture of the *cis*- and *trans*-simple complexes at the lowest possible reaction temperature:

$$(PPr_3)_2PtCl_2 + PtCl_2 = (PPr_3)_2Pt_2Cl_4$$

Dichlorobis(tri-*n*-propylphosphine)-$\mu\mu'$-dichlorodiplatinum is thus prepared at 165° (Chatt, *J.*, 1950, 2301), and the arsenic analogue at 125°, the temperature being gradually raised to 150° as reaction proceeds. This reaction has also been applied to prepare the di-*n*-propyl sulphide bridged derivative at 120—150°, but neither *p*-toluidine nor tertiary stibine bridged complexes could be prepared by this method.

A second general method is provided by the reaction of the ligand with a solution of ethyleneplatinous chloride at or below room temperature:

$$(C_2H_4)_2Pt_2Cl_4 + 2L = L_2Pt_2Cl_4 + 2C_2H_4$$

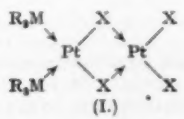
The yields are not good, and L_2PtCl_2 is also a major product. Dichlorobis(tri-*n*-propylstibine)-$\mu\mu'$-dichlorodiplatinum has been prepared by this method, as has also the phosphorus analogue, but tri-*n*-propylamine gave only a yellow solution which on concentration under reduced pressure at room temperature yielded an intractable, unstable yellow oil.

The three Group V derivatives form a well-graded series, the properties of which are summarised below. They are soluble in many organic solvents—acetone, alcohol, benzene, chloro-

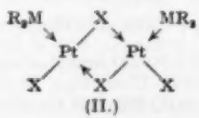
Substance.	M. p.	Colour.	Soly. in org. solvents.	Stability.
$(PPr_3)_2Pt_2Cl_4$	180—182°	Pale orange	Increases from the phosphine to the stibine complex	Stable
$(AsPr_3)_2Pt_2Cl_4$	156·5—157·5	Reddish-orange		Decomp. very slowly in boiling alcohol
$(SbPr_3)_2Pt_2Cl_4$	133—134 (decomp.)	Reddish-orange		Decomp. rapidly in boiling EtOH, $COMe_2$, or CCl_4

form, etc.—but are rather less soluble and much paler in colour than the corresponding palladium compounds, which otherwise they resemble closely.

The above is the first stibine bridged complex to be isolated, and in view of its low stability it seems doubtful whether bridged stibine complexes of any other metallic chloride will exist at room temperature. No attempt was made to prepare the tri-*n*-propylbismuthine analogue.



(I.)



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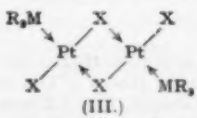


(III.)

Search for Geometric Isomerism amongst these Halogen-bridged Complexes.—Pfeiffer (*loc. cit.*) pointed out the possibility that bridged complexes of this type might exist in three isomeric forms (I), (II), and (III), but there is no proved case where such isomers containing platinum or any other metal have been isolated. On the basis of the empirical knowledge that the simple platinous complexes show geometric isomerism to a greater extent than any other, it has often been suggested that such isomers would be found in the platinous series. Dichloro-bis(tri-*n*-propylphosphine)-$\mu\mu'$-dichlorodiplatinum, the most stable of these bridged complexes, has been

prepared by the following four methods at temperatures ranging from −70° to 165° in an attempt to obtain such isomers:

(1) (*a*) *trans*-$(PPr_3)_2PtCl_2 + PtCl_2 = (PPr_3)_2Pt_2Cl_4$ (165°)
(*b*) *cis*-$(PPr_3)_2PtCl_2 + PtCl_2 = (PPr_3)_2Pt_2Cl_4$ (165°)
(2) $(C_2H_4)_2Pt_2Cl_4 + 2PPr_3 = (PPr_3)_2Pt_2Cl_4 + 2C_2H_4$ (−70° to 10°)
(3) $(PPr_3)_2Pt_2Cl_4 + 2SnCl_2 = (PPr_3)_2Pt_2Cl_4 + 2SnCl_4$ (20°)

Careful fractionation of the products has revealed no evidence of isomerism.

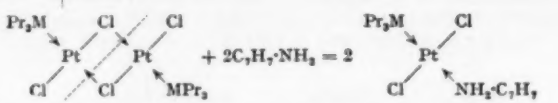
I am indebted to C. W. Bunn and R. de P. Daubeny for a powder *X*-ray examination of the above bridged phosphine complex. They found that it is isomorphous with, and has the same unit cell size as, the corresponding palladium compound (Mann and Purdie, *J.*, 1936, 884). It must thus have the *trans*-symmetrical structure (III), which has been assigned to this class of bridged palladium compound (Mann and Wells, *loc. cit.*). If either of the *cis*-isomers (I) or (II) had been produced in any of the above reactions, it is unlikely that they would have escaped detection because their dipole moments would be sufficiently high to render them much less soluble than this symmetrical isomer in non-polar solvents.

The above bridged tetrachloride, $(PPr_3)_2Pt_2Cl_4$, was also converted into the orange tetrabromide by boiling it in aqueous-alcoholic solution with 100% excess of ammonium bromide, and almost quantitatively into the bright red tetraiodide by treating its acetone solution with sodium iodide in acetone. The tetrabromide was more conveniently prepared directly by method (I), using crude bis(tri-*n*-propylphosphine)dibromoplatinum and platinous bromide. Again no evidence of isomerism was found.

If this isomerism exists amongst halogen-bridged complexes, the only remaining compounds which might show it are the bridged complexes of platinous halides with primary amines $(R{\cdot}NH_2)_2Pt_2Cl_4$. Compounds of this type with any metal are, however, almost unknown, and no general synthetic method of preparation has been developed.

Reactions of the Above Bridged Complexes with p-*Toluidine and with* 2 : 2′-*Dipyridyl.*—For comparison with the reactions of the bridged palladium compounds, *p*-toluidine and 2 : 2′-dipyridyl were chosen as typical reagents.

Reaction with p-*toluidine.* With *p*-toluidine at room temperature each of the three bridged compounds reacted immediately:



Only the *trans*-isomer was isolated in each case. This result is exactly analogous to the reactions of the palladous bridged complexes, but contrasts with the results of Rosenheim and Levy (*Z. anorg. Chem.*, 1905, **43**, 35) who obtained white and yellow isomeric substances, presumably *cis*- and *trans*-isomers, by splitting the ethyl phosphite complex, $[(EtO)_3P]_2Pt_2Cl_4$, with primary amines. Of the unsymmetrical products, $MR_3,C_7H_7{\cdot}NH_2,PtCl_2$, the phosphorus and the arsenic compound are stable but the stibine complex decomposes in a vacuum at 0·1 mm. pressure.

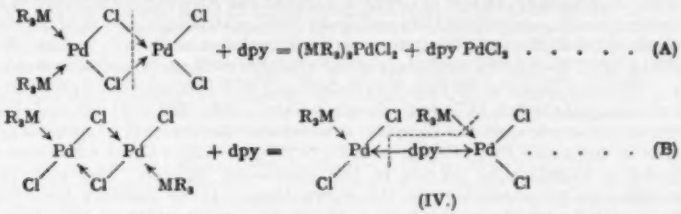
Although we were unable to prepare tri-*n*-propylaminoplatinous chlorides, either simple or bridged, because the products of every reaction tried decomposed rapidly, we obtained tri-*n*-propylaminotri-*n*-propylphosphinedichloroplatinum as a stable, beautifully crystalline yellow solid closely resembling *trans*-$(PPr_3)_2PtCl_2$, by the reaction

$$(PPr_3)_2Pt_2Cl_4 + 2NPr_3 = 2(PPr_3,NPr_3PtCl_2)$$

This is apparently the first complex of a trialkylmono-amine with platinous salts ever recorded; although Jensen ("Om de Koordinativt Firegyldige Metallers Stereokemi," Reitzels Forlag, Copenhagen, 1937; *Z. anorg. Chem.*, 1936, **229**, 228) claims to have prepared some, he has never published details. Evidently, tertiary amine platinous complexes are very unstable as compared with their phosphorus and even antimony analogues. The less stable tripropylarsine–tripropylamine analogue was also prepared. When tri-*n*-propylbismuthine was added to a benzene solution of the bridged phosphine tetrachloride there was no change in colour or other evidence of the formation of tri-*n*-propylbismuthinetri-*n*-propylphosphinedichloroplatinum but fairly rapid reduction to metallic platinum occurred.

Reactions with 2 : 2′-*dipyridyl.* (i) In the palladium series the reaction with 2 : 2′-dipyridyl was apparently a vertical splitting of the *cis*-isomer type (I), as in (A), but this explanation was

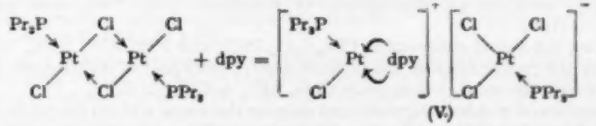
later abandoned in favour of the scheme (B). It was supposed that the dipyridyl first reacted, each nitrogen atom independently, splitting the bridge to form an unstable intermediate (IV) which, because of the strongly chelating tendency of the dipyridyl, splits, as shown by the broken line, to give the products of equation (A) (Chatt, Mann, and Wells, *J.*, 1938, 2089).



(IV.)

(ii) The reaction of dipyridyl with the platinum bridged complexes was of particular interest because the intermediate, which has not the structure (IV) but is ionic, was isolated from the reaction with both the phosphine and arsine bridged complexes. The stibine complex, however, reacted rapidly and completely after the manner of the palladium complexes.

(iii) The reaction of dipyridyl with the phosphine bridged complex occurred as follows in benzene solution :



(V.)

The salt, tri-*n*-propylphosphinedipyridylchloroplatinum tri-*n*-propylphosphinetrichloroplatinite (V), separated almost quantitatively in beautiful yellow leaflets, readily recrystallised from alcohol. It is dissociated in freezing nitrobenzene solution as shown by molecular-weight determination; the electrical conductivity in nitrobenzene solution at 25° followed Ostwald's dilution law fairly well over the concentration range 2·7—50 × 10^{-3} mols. per litre. The best value of Λ_∞ thus calculated was 18·95 mhos. At very low concentrations, however, some second weak ionisation must become significant because the molar conductivity rose rapidly to 30 mhos as the concentration was decreased from 0·27 to 0·013 × 10^{-3} mols. per litre.

The reaction is thus exactly analogous to that found by Foss and Gibson (*J.*, 1949, 3063) for the reaction of dipyridyl with diethylmonobromogold. The analogy is carried further in that a second molecule of dipyridyl, which might be expected to react with the salt (V), yielded

$$[PPr_3,dpy,PtCl]^+[PPr_3PtCl_3]^- + dpy = 2[PPr_3,dpy,PtCl]^+Cl^-$$

an equilibrium from which only the starting materials, (V) and dipyridyl, could be isolated. The same behaviour was observed with the gold salt $[dpy,Et_2Au]^+[Et_2AuBr_2]^-$.

(iv) The arsine bridged complex reacts with dipyridyl in an analogous manner, except that the reaction

$$(AsPr_3)_2Pt_2Cl_4 + dpy = (AsPr_3)_2PtCl_2 + dpy\ PtCl_2$$

occurs as a very minor side reaction and the arsine salt $[AsPr_3,dpy,PtCl]^+[AsPr_3,PtCl_3]^-$ is contaminated with a few small yellow and red needles of dipyridyldichloroplatinum. This salt is much less stable than its phosphine analogue. In boiling alcohol it decomposes rapidly :

$$[AsPr_3,dpy,PtCl]^+[AsPr_3,PtCl_3]^- = (AsPr_3)_2PtCl_2 + dpy\ PtCl_2\downarrow$$

In 2·5 × 10^{-3}M-nitrobenzene solution it has a molecular conductivity (extrapolated to zero time) of 17·7 mhos at 25°, but the conductivity falls to half its value in 90 mins. owing to the above decomposition. In more concentrated nitrobenzene solution at room temperature, long brilliant red needles of $dpy,PtCl_2$ separate as the decomposition proceeds. These then change into the yellow form spontaneously.

(v) The only reaction observed with the stibine bridged complex was :

$$(SbPr_3)_2Pt_2Cl_4 + dpy = (SbPr_3)_2PtCl_2 + dpy\ PtCl_2\downarrow$$

and this is complete in about five minutes. The dpy,$PtCl_2$ was deposited almost entirely in the red form. The stibine salt analogous to (V) is probably an unstable intermediate, thus bringing this reaction into line with those observed in the phosphorus and the arsenic series. The same mechanism is also probable for the corresponding reactions in the palladium series.

The Co-ordinating Affinity of Group V Ligands and Ethylene.—The order of stabilities of the phosphine, arsine, and stibine salts analogous to (V) is striking evidence of the rapidly decreasing strength of the $R_3M \longrightarrow Pt$ bond as we pass along the series M = P, As, and Sb. This order is observed in all the known complexes of the trialkyls of these elements, and may be universally true. When we consider the failure to obtain simple or bridged complexes of tri-*n*-propylamine, and the complete failure of Jensen (*Z. anorg. Chem.*, 1936, **229**, 234) and ourselves to obtain any platinous tertiary bismuthine complex, it seems that the strength of co-ordination to platinous salts is in the order $PR_3 > AsR_3 > SbR_3 > NR_3 > BiR_3$. Great care must be exercised in assigning a co-ordinating affinity in this qualitative manner. This may be illustrated by attempting to place ethylene in the above series. If we consider the bridged complexes $L_2Pt_2Cl_4$, ethyleneplatinous chloride, $(C_2H_4)_2Pt_2Cl_4$, decomposing at 180—190°, is more stable than its analogous propylstibine complex, decomposing at 133—134°. In solution also, the stibine complex has the lower stability, whereas there is no question that the arsine complex has a much greater stability; the co-ordinating affinity appears to be $AsPr_3 > C_2H_4 > SbPr_3$.

When we consider the only known forms of the simple complexes L_2PtCl_2 the order is reversed; the stibine complex melts without decomposition at 80—81° (Jensen, *Z. anorg. Chem.*, 1936, **229**, 247), whereas the ethylene complex decomposes at −10° (Chatt and Wilkins, *Nature*, 1950, **165**, 859), even in an atmosphere of ethylene. The order now appears to be $SbPr_3 > C_2H_4 > NPr_3$.

If we consider the mixed compounds $PPr_3,C_2H_4,PtCl_2$ and $PPr_3,NPr_3,PtCl_2$, we have so far failed to prepare the former because the product always loses part of its ethylene, but the latter is readily prepared; the order thus appears to be $NPr_3 > C_2H_4 > BiPr_3$.

Thus the position of ethylene depends, not only on the metal and on its valency, but also on the class of compound we choose for the comparison. The strength of co-ordination of any particular ligand is thus very sensitive to the nature of the other groups attached to the metal, and it appears misleading to place ligands in order of co-ordinating strengths either generally or with reference to a particular metal, unless we also define minutely the type of complex.

As a further example of co-ordinating affinity, the above orders can be contrasted with the series $NMe_3 > PMe_3 > AsMe_3 > C_2H_4$ (private communication from Herbert C. Brown, Purdue University; Chatt, *J.*, 1949, 3340) observed for co-ordination to trimethylborine, which appears to be fundamentally different from co-ordination to platinum(II) (Chatt, *Nature, loc. cit.*).

Experimental.

* Microanalysis by Mr. W. Brown, Butterwick Research Laboratories, † by Mr. H. R. Thomas, Imperial Chemical Industries Limited, Paints Division, Slough, ‡ by Dr. G. Weiler and Dr. F. B. Strauss, Oxford, § by Mr. F. Weisser, Basle.

Preparation of Dichlorobis(tri-n-propylarsine)-μμ'-dichlorodiplatinum.—This *compound* was prepared in the same manner as its phosphorus analogue at 125—150° (Chatt, *J.*, 1950, 2306) and recrystallised from alcohol; yield 41%, m. p. 156·5—157·5° (Found: C*, 23·0; H*, 4·7. $C_{18}H_{42}Cl_4As_2Pt_2$ requires C, 23·0; H, 4·5%). The corresponding bright yellow bridged di-*n*-propyl sulphide compound, prepared by the same method at 120—150° and recrystallised from acetone, had m. p. 194—197° (decomp.). It appears to be identical with Jensen's product (*Z. anorg. Chem.*, 1935, **225**, 125), obtained by reaction of *cis*-$(SPr_2)_2PtCl_2$ with aqueous alcoholic potassium chloroplatinite (Found: C*, 18·7; H*, 3·7. Calc. for $C_{12}H_{28}Cl_4S_2Pt_2$: C, 18·75; H, 3·7%).

Preparation of Dichlorobis-(tri-n-propylstibine)-μμ'-dichlorodiplatinum.—Solutions of tri-*n*-propylstibine (3·5 g., 2 mols.) in acetone (15 c.c.) and ethyleneplatinous chloride, $(C_2H_4PtCl_2)_2$ (4·10 g., 1 mol.) in acetone (50 c.c.) were prepared under a nitrogen atmosphere and cooled to −70°. The stibine solution was then slowly added, with swirling, to the solution of the platinum compound, through a syphon tube operated by the nitrogen pressure. The mixed solution was now allowed to warm to room temperature, and the acetone removed under 15 mm. pressure. A residual, sticky, orange-red solid was extracted with a little ethyl acetate, and the solid residue of the *complex* was quickly recrystallised from acetone; yield 2·10 g., m. p. 133—134° (decomp.) (Found: C*, 20·75; H*, 4·05. $C_{18}H_{42}Cl_4Pt_2Sb_2$ requires C, 20·9; H, 4·1%).

Preparation of Dichlorobis-(tri-n-propylphosphine)-μμ'-dichlorodiplatinum (Tetrachloro-compound).—Methods (1) and (3) (see p. 654) are described by Chatt (*J.*, 1950, 2305). Method (2) is analogous to the preparation of the bridged stibine complex. Ethyleneplatinous chloride $(C_2H_4PtCl_2)_2$ (2·8 g.) in acetone (50 c.c.) was treated at −63° with an acetone (10 c.c.) solution of tri-*n*-propylphosphine (1·51 g., 2 mols.). There was change of colour and yellow crystals separated. These dissolved as the solution warmed to room temperature and a little gas was evolved. The solution was now evaporated at 15 mm. pressure to about 8 c.c., whereupon slow separation of an amorphous-looking, rather dirty solid set in. This was removed, but the slow separation of the solid continued and overnight about 90 mg. of light yellowish

material were obtained. It was insoluble in all solvents tried and blackened rapidly in boiling water and in boiling dioxan. It was purified as far as possible by thorough extraction with acetone. When heated in a m. p. tube it showed no change except gradual darkening, becoming grey at 150° and black at 160°. Its analysis corresponded to diethylenedichloroplatinum contaminated with 10·75% of platinum (Found: C‡, 13·4; H‡, 2·1; Cl‡, 19·7; Pt‡, 65·05. Calc. for $C_4H_8Cl_2Pt$: C, 14·9; H, 2·5; Cl, 22·0; Pt, 60·6%) and it may be the *cis*-isomer, but is possibly a polymeric substance. It effervesces at once with potassium cyanide solution, as do all ethyleneplatinous complexes. If we assume the sample contained 10·75% of metallic platinum as impurity, the corrected analysis figures are: C, 15·0; H, 2·31; Cl, 22·1; Pt, 60·8%. We were unable to obtain purer material or appreciably better yields, except of inferior material, for a more thorough investigation. The substance is interesting because it is the first example of what may possibly be a simple non-ionic bisolefin complex. The mother-liquor from which the material had separated, on standing for a week, deposited a further 0·75 g. of black insoluble material. This was removed, and the mother-liquor taken to dryness under 15 mm. pressure. The *trans*-$(PPr_3)_2PtCl_2$ contained in it was extracted with ether, then the residue, recrystallised from acetone, yielded 0·7 g. of pure tetrachloro-compound. The ether extract was evaporated to dryness, and the residue recrystallised from alcohol, yielding 0·8 g. of pure *trans*-$(PPr_3)_2PtCl_2$, m. p. alone and mixed with an authentic specimen 83—85°. This preparation was repeated, but the products were worked up rapidly; instead of 0·75 g. of black insoluble material, 0·66 g. of unchanged ethyleneplatinous chloride was recovered. In a further experiment carried out in benzene at room temperature, in spite of a careful search no evidence of $C_2H_4.PPr_3.PtCl_2$, *cis*-$(PPr_3)_2PtCl_2$, or isomers of the tetrachloro-compound, $(PPr_3)_2Pt_2Cl_4$, was obtained.

Preparation of trans-*Bis*(*tri*-n-*propylphosphine*)*dibromoplatinum*.—This was prepared in the same way as the chloro-compound by reaction of the phosphine (2 mols., 2·3 g.) with aqueous potassium bromoplatinite (1 mol.) (Jensen, *Z. anorg. Chem.*, 1936, **229**, 240). The product was almost entirely soluble in ether, leaving a small white residue; this after recrystallisation from methyl alcohol had m. p. 160—161·5° and is presumably the *cis*-isomer, but there was insufficient for analysis. The ethereal extract on evaporation yielded a yellow residue of trans-*bis*(*tri*-n-*propylphosphine*)*dibromoplatinum*, which was pure after three recrystallisations from methyl alcohol and had m. p. 96—97° (1·5 g.) (Found: C†, 31·9; H†, 6·2. $C_{18}H_{42}Br_2P_2Pt$ requires C, 32·0; H, 6·3%).

Preparation of Dibromobis-(*tri*-n-*propylphosphine*)-μμ′-*dibromodiplatinum* (*Tetrabromo-compound*).—Prepared in the same way as its chlorine analogue (method 1) at 210°, the *tetrabromo*-compound was obtained in orange crystals, m. p. 167—168° (from acetone) (Found: C†, 20·9; H†, 4·15. $C_{18}H_{42}Br_4P_2Pt_2$ requires C, 21·0; H, 4·1%). It was also obtained by replacing the chlorine in its chlorine analogue by bromine: 0·46 g. (8 mols.) of ammonium bromide in water (1 c.c.) was added to 0·5 g. (1 mol.) of the tetrachloro-compound in alcohol (15 c.c.), and the mixture boiled under reflux for 1½ hours. The product was taken to dryness at 15 mm. pressure, and the residue extracted with boiling water. The orange residue, recrystallised twice from alcohol, was the pure tetrabromo-compound, m. p. 167—168° (0·3 g.).

Preparation of Di-iodobis(*tri*-n-*propylphosphine*)-μμ′-*di-iododiplatinum* (*Tetraiodo-compound*).—Sodium iodide (2·14 g., 4·5 mols.) in acetone (20 c.c.) was added to a solution of the tetrachloro-compound (2·68 g., 1 mol.) in acetone (120 c.c.), and the whole boiled under reflux for 40 minutes. The solution was filtered hot, and the filtrate deposited 2·07 g. of almost pure *tetraiodo*-compound on cooling. Recrystallised (acetone), it had m. p. 200—201° (yield 1·42 g.) (Found: C‡, 17·7; H‡, 3·4; Pt†, 32·0, 32·2. $C_{18}H_{42}I_4P_2Pt_2$ requires C, 17·7; H, 3·5; Pt, 32·0%). A further 2·1 g. of crude product were obtained from the mother-liquors.

Reaction of p-*Toluidine with the Bridged Tri*-n-*propylphosphine, -arsine, and -stibine Tetrachloro-compounds*.—The reaction with the phosphine complex has already been described (Chatt, *J.*, 1950, 2309). The reactions with the arsine and stibine compounds in benzene were exactly analogous. trans-p-*Toluidinotri*-n-*propylarsinedichloroplatinum* (recryst. from ligroin, b. p. 80—100°; yield 75%) was obtained in well-formed, yellow, granular crystals, m. p. 94° (Found: C*, 33·3; H*, 5·1; N*, 2·55. $C_{16}H_{30}NCl_2AsPt$ requires C, 33·3; H, 5·2; N, 2·4%). The light orange *stibine* analogue (recryst. from ligroin, b. p. 60—80°; yield 37%) had m. p. 69°. A sample decomposed on attempted drying at 0·1 mm. pressure, but was dried in a vacuum-desiccator (15 mm.) over sulphuric acid (Found: C*, 31·0; H*, 4·8; N*, 2·6. $C_{16}H_{30}NCl_2PtSb$ requires C, 30·8; H, 4·8; N, 2·2%).

Preparation of Tri-n-*propylaminetri*-n-*propylphosphinedichloroplatinum*.—Tripropylamine (0·83 g., 2 mols.) in benzene (5 c.c.) was added to the tetrachloro-compound (2·48 g., 1 mol.) in benzene (45 c.c.) at 25°. There was a change of colour from orange to yellow and a rise of temperature of 2·5°. Evaporation at 15 mm. pressure and room temperature gave the yellow crystalline *complex*, which was pure after one recrystallisation from methyl alcohol, and then had m. p. 114—115° (yield 1·72 g.) (Found: C‡, 38·0; H‡, 7·1; N*, 2·4. $C_{18}H_{42}NCl_2PPt$ requires C, 38·0; H, 7·4; N, 2·5%). The yellow *tripropylarsine* analogue, similarly obtained, had m. p. 104—105° (decomp.), dependent on the rate of heating (Found: C*, 35·1; H*, 6·8; N*, 2·4. $C_{18}H_{42}NCl_2AsPt$ requires C, 35·2; H, 6·9; N, 2·3%). In an attempt to obtain tri-*n*-propylbismuthinetri-*n*-propylphosphinedichloroplatinum in the same manner, the reaction mixture darkened and finally deposited metallic platinum during the evaporation at room temperature. No pure substance was isolated.

Reaction of 2 : 2′-*Dipyridyl with the Bridged Tri*-n-*propyl-phosphine, -arsine, and -stibine Tetrachloro-compounds*.—The phosphine tetrachloro-compound (1 g., 1 mol.) in benzene (25 c.c.) was treated with 2 : 2′-dipyridyl (0·183 g., 1 mol.) in benzene (5 c.c.) at room temperature. The colour immediately changed to yellow and pure *tri*-n-*propylphosphinedipyridylchloroplatinum tri*-n-*propylphosphinetrichloroplatinite* started to separate in beautiful, bright yellow scales. Next morning, 1·04 g. of product were filtered off. It melted sharply with decomposition anywhere in the range 170—180° according to the rate of heating; recrystallisation from acetone or alcohol did not improve the product (Found: C*, 33·2; H*, 4·95; N*, 2·84%; *M*, cryoscopically in nitrobenzene, 671 in 0·818% and 735

in 1·786% solution. $C_{18}H_{50}N_2Cl_4P_2Pt_2$ requires C, 33·35; H, 5·0; N, 2·78%; *M*, 1009). The values of *M* correspond to a dissociation (α) of 50·4% and 37·3%, respectively. The molecular conductivity (Λ_v) at 25°, measured with a Mullard conductance bridge, varies with molar concentration as in the table, which also shows the values of Ostwald's dissociation constant, *K*, calculated on the basis that Λ_∞ = 18·95. Values recorded in heavy type are constant to the accuracy of the measurements.

Concn. × 10^4	0·135	0·270	2·70	13·5	26·85	78·6	131	196·5	268·5	393	524	1026	1861
Λ_v, mhos ...	30·6	28·1	21·8	18·6	16·75	13·9	12·5	10·9	9·98	9·15	8·00	5·535	3·72
$K \times 10^3$ ...	—	—	—	77	18·1	**15·9**	**16·8**	**15·4**	**15·7**	**17·4**	**16·2**	12·4	8·9

A solution in nitrobenzene showed no change in conductivity after 3 days.

The *arsine* analogue, similarly prepared, was contaminated with a little dipyridyldichloroplatinum. It was purified by dissolution in chloroform at room temperature, filtration, and reprecipitation of the pale yellow, slightly orange product with ethyl alcohol. It blackens on heating to 260—280°, and decomposes on attempted recrystallisation from hot solvents (Found: C*, 30·65; H*, 4·5; N*, 2·75. $C_{18}H_{50}N_2Cl_4As_2Pt_2$ requires C, 30·65; H, 4·6; N, 2·55%).

The molar conductivity of a 2·5 × 10^{-3}M.-solution of the arsine salt in nitrobenzene solution, initially almost identical with that of the phosphine salt, decreases rapidly with time; then, as it approaches zero, only very slowly. The variation of molar conductivity with time at 25° is :

Time, mins.	0	6	8	12	16	30	60
Λ_v, mhos	17·7 extrap.	16·8	16·4	15·8	15·2	13·2	10·6

Time, mins.	100	175	393	536	1108	2843	10·5 days
Λ_v, mhos	8·31	5·76	2·77	1·98	0·857	0·356	0·185

*Attempt to prepare Tri-*n*-propylphosphine-ethylenedichloroplatinum,* $PPr^n_3C_2H_4PtCl_2$.—The first reaction tried was $(C_2H_4)_2Pt_2Cl_4 + 2PPr^n_3 = 2C_2H_4,PPr^n_3PtCl_2$, as described on p. 657, but no sign of formation of the desired product was obtained.

The reaction of tripropylphosphine with aqueous potassium ethylenetrichloroplatinite was partially successful: $(C_2H_4)_2Pt_2Cl_4$ was dissolved in 50 c.c. of a solution of potassium chloride (0·76 g., 2 mols.) in water, and filtered; propylphosphine (1·61 g., 2 mols.) was next added together with a little alcohol used to wash out the propylphosphine from its container, and the whole shaken together for ½ hour. Some ethylene was evolved, and a yellow solid separated and was filtered off and dried (yield 3·15 g.; m. p. 97—100°). Extraction with ether removed a portion of *trans*-$(PPr^n_3)_2PtCl_2$ (m. p. 85—87° alone or mixed with an authentic specimen), leaving an ether-insoluble yellow substance, m. p. 105—111° (efferv.) for different preparations. This substance was too unstable to be purified by recrystallisation. It was insoluble in ether and very soluble in acetone, and very small quantities could be recrystallised quickly from ethyl alcohol or carbon tetrachloride without improvement in purity. In attempts to recrystallise larger quantities, only the bridged complex $(PPr^n_3)_2Pt_2Cl_4$, m. p. 181·5—183° alone or mixed with an authentic specimen, separated from the cold solution. In composition the product approximated to the *molecular compound* $(PPr^n_3)_2PtCl_2,PPr^n_3,C_2H_4PtCl_2$ (Found: C‡, 34·1; H‡, 6·3. $C_{19}H_{47}Cl_4P_3Pt_2$ requires C, 33·5; H, 6·5%).

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141. *Organo-lead Compounds. Part IV.* (a) *A New Method for preparing Diethyl-lead Salts.* (b) *Derivatives of Mixed Plumbanes.*

By R. HEAP, B. C. SAUNDERS, and G. J. STACEY.

An account is given of methods of obtaining diethyl-lead salts, including a new unambiguous preparation which consists in treating diethyl-lead sulphite, $PbEt_2SO_3$, with the appropriate acid. The ready disproportionation of some dialkyl-lead salts is described.

Some derivatives of mixed plumbanes are described, and their sternutatory properties recorded.

WHEN a plumbane is treated with an acid and silica gel, the trialkyl-lead salt (cf. I) is usually produced in good yield (Saunders and Stacey, Part I, *J.*, 1949, 919). We have found, however, that sometimes a dialkyl-lead salt of type (II) is formed, and occasionally a mixture of products is obtained: $PbEt_4 + Me{\cdot}CO_3H = PbEt_3{\cdot}O{\cdot}COMe$ (I) + C_2H_6, $PbEt_4 + 2Ph{\cdot}CO_2H = PbEt_2(O{\cdot}COPh)_2$ (II) + $2C_2H_6$.

It is not very clear what governs this difference in behaviour. Apart from time of heating, temperature, and presence of catalyst, in some cases the nature of the acid seems to be one of the factors concerned. Frequently, the analyses of trialkyl-lead salts and of the corresponding dialkyl-lead salts are close and therefore independent methods of preparation are described.

The constitution of the trialkyl-lead salts is readily established by neutralisation of a trialkyl-lead hydroxide with the appropriate acid (Part I, *ibid.*; Heap and Saunders, Part II, *J.*, 1949, 2983). As a starting point for an independent method for preparing diethyl-lead salts we first selected diethyl-lead dichloride. This was prepared in pure condition by a modification of Gilman and Robinson's method (*J. Amer. Chem. Soc.*, 1930, **52**, 1975), and was then free from both triethyl-lead chloride and plumbous chloride. Diethyl-lead dichloride reacted with metallic salts to give the corresponding diethyl-lead salts; *e.g.*, silver chloroacetate gave diethyl-lead bischloroacetate, $PbEt_2(O{\cdot}CO{\cdot}CH_2Cl)_2$. This type of reaction was not wholly successful because of the difficulty of finding suitable solvents. The reaction was therefore performed heterogeneously in water, and although a pure product could be obtained, care had to be taken to avoid disproportionation (see p. 660).

Although the conversion of triethyl-lead chloride into the hydroxide by aqueous sodium hydroxide is well known (Part I, *loc. cit.*), the corresponding conversion of diethyl-lead dichloride into the dihydroxide has not previously been investigated. The latter reaction did not, however, proceed in a similar manner, because the dihydroxide, $PbEt_2(OH)_2$, was readily soluble in the alkaline layer. Under the correct conditions, however, it could be crystallised from the alkaline layer and purified by recrystallisation from a small volume of water at a low temperature. It was then obtained as the efflorescent hexahydrate, $PbEt_2(OH)_2,6H_2O$, which was readily dehydrated *in vacuo* at room temperature to the corresponding oxide $PbEt_2O$. The hydrated dihydroxide reacted readily with the appropriate acid, giving the dichloride, the diacetate, and the bischloroacetate. Hence this dihydroxide could be used as a basis for a general method of preparing diethyl-lead salts, were it not for the inconvenience involved in isolating it from alkaline solutions. The action of moist silver oxide in place of sodium hydroxide on the dichloride was investigated, but although excess of silver oxide was used the reaction did not proceed rapidly or completely, and the dihydroxide was difficult to isolate from solution in the presence of unchanged diethyl-lead dichloride.

No evidence was obtained to distinguish between the two possible formulæ $PbEt_2O,7H_2O$ and $PbEt_2(OH)_2,6H_2O$, but the latter was adopted merely to afford a parallel with triethyl-lead hydroxide. In quantitative dehydration experiments, it was not possible to stop precisely at the dihydroxide (anhydrous stage).

We next investigated the action of sulphur dioxide on tetraethyl-lead in ethereal solution. This reaction is quoted by Goddard (Friend's "Textbook of Inorganic Chemistry," Vol. XI, i, p. 333) as giving diethyl sulphone, but no mention is made of the fate of the lead. Employing the conditions described on p. 662, we found that the hitherto undescribed diethyl-lead sulphite, $PbEt_2SO_3$, was precipitated quantitatively as an amorphous powder. It dissolved readily in dilute mineral acids and in weak acids with the evolution of sulphur dioxide. In this way diethyl-lead dichloride, dibenzoate, bischloroacetate, bistrichloroacetate, ditoluene-*p*-sulphonate, ditoluene-*o*-sulphonate, and bisthioacetate were obtained. These compounds were highly crystalline, and aqueous solutions (where obtainable) gave cream-coloured precipitates with hydrogen sulphide, showing that they were uncontaminated with plumbous compounds (see p. 660).

The diethyl-lead compounds mentioned above, when dispersed at concentrations of 1 part in 10^6 in a testing-chamber, did not exert any appreciable sternutatory effects on observers. These compounds were therefore Grade 0 (see Part I, *loc. cit.*, for grading). Incidentally, this physiological test could be used to prove the absence in these compounds of the corresponding triethyl-lead compounds, which possess powerful sternutatory properties at 1 in 10^7 and are easily detectable at much greater dilutions.

A complete series of salts was obtained from tetraethyl-lead and thioacetic acid under appropriate conditions. Thioacetic acid reacted with tetraethyl-lead in the cold to give triethyl-lead thiolacetate, $PbEt_3{\cdot}S{\cdot}COMe$, identical with the product obtained by the action of thioacetic acid on triethyl-lead hydroxide. At 100°, thioacetic acid and tetraethyl-lead in the absence of silica gel gave a mixture of triethyl-lead thiolacetate, diethyl-lead bisthiolacetate (identical with the compound from diethyl-lead sulphite and thioacetic acid), and plumbous thioacetate, whereas in the presence of silica gel the sole product was plumbous thiolacetate.

In many of the preparations of diethyl-lead salts, difficulty was caused by decomposition, with the production of plumbous compounds, particularly on heating. We therefore

investigated the decomposition of diethyl-lead bischloroacetate in hot water and it seemed that disproportionation took place into plumbous chloroacetate, triethyl-lead chloroacetate, and ethyl chloroacetate:

$$2PbEt_2(O{\cdot}CO{\cdot}CH_2Cl)_2 = PbEt_2{\cdot}O{\cdot}CO{\cdot}CH_2Cl + Pb(O{\cdot}CO{\cdot}CH_2Cl)_2 + CH_2Cl{\cdot}CO_2Et \quad . \; . \quad (A)$$

Such a reaction taking place in a single stage seems unlikely, and a possible mechanism is as follows. From cryoscopic measurements we have shown that many diethyl- and triethyl-lead salts are ionised to a considerable extent in aqueous solution. Equation (A) can then be written as the ionic equation (B) where A = acidic ion. It can be assumed that, in the diethyl-lead

$$Et_2Pb^{++} + A^- = Et_2Pb^+ + Pb^{++} + EtA \quad . \; . \; . \; . \; . \; . \; . \; . \quad (B)$$

ion, the two ethyl groups are attached by weak bonds which are susceptible to strain such as could be produced by an electric field set up by the other ions present. This ion may be written as $Et\overset{\delta+}{\frown}Pb\overset{\delta-}{\frown}Et^{++}$. Under sufficient strain the rupture of one of the Pb–Et bonds becomes probable and an unstable stage may be represented thus:

$$AEt + {:}Pb^+{-}Et + Et_2Pb^{++} \quad . \; . \; . \; . \; . \; . \; . \; . \; . \; . \quad (C)$$

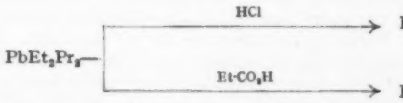
In the highly reactive unstable :Pb–Et, the remaining ethyl group would be expelled by the lead atom to restore electron stability, and the final products will be $AEt + Pb^{++} + Et_2Pb^+$.

Diethyl-lead bischloroacetate can be recrystallised from cold (but not hot) water and also from hot absolute ethyl alcohol without disproportionation. A similar disproportionation of di-*n*-propyl-lead diacetate was observed when its aqueous-alcoholic solution was evaporated on a water-bath. At room temperature negligible disproportionation took place. Diethyl-lead dibenzoate does not dissolve in water and was unaffected by boiling water but, when it was heated alone above its melting point, the odour of ethyl benzoate was observed.

The lability of the ethyl radicals in organo-lead compounds is probably the cause of the instability frequently encountered, and in this connexion reference may be made to production of tetraethyl-lead from triethyl-lead chloride and certain sodium compounds (*e.g.*, sodium nitromethane, see Part II, *loc. cit.*).

In general, the three classes of lead salt are readily distinguished in aqueous solution. The plumbous ion gives a heavy black precipitate with hydrogen sulphide, insoluble in organic acids and dilute mineral acids. Diethyl-lead salts of weak acids, when soluble in water, give a flocculent cream-coloured precipitate with hydrogen sulphide or ammonium sulphide; this precipitate dissolves immediately in dilute mineral acids. Under similar conditions triethyl-lead salts of weak acids give a milky-white precipitate also soluble in dilute mineral acid. Thus the hydroxide or acetate will give precipitates with hydrogen sulphide, whereas the chloride does not unless the solution is buffered with sodium acetate or rendered faintly alkaline with ammonia.

Derivatives of Mixed Plumbanes.—In our search for trialkyl-lead salts of high sternutatory power, we investigated compounds in which the alkyl groups attached to the lead atom were not all the same. A convenient starting point was the mixed plumbane, diethyldi-*n*-propyl-lead, which on treatment with a strong acid appeared to lose one ethyl group, whereas a weaker acid appeared to eliminate one propyl group. It should be emphasised, however, that the analytical figures of the likely products lie very close together, thus rendering identification difficult:



The action of hydrogen chloride falls into line with Grüttner and Krause's observation (*Ber.*, 1917, **50**, 202) that halogens displace first the lightest group.

From ethyldipropyl-lead chloride and the sodium derivative of toluene-*p*-sulphonamide we obtained *N*-(ethyldipropylplumbi)toluene-*p*-sulphonamide, $C_6H_4Me{\cdot}SO_2{\cdot}NH{\cdot}PbEtPr_2$, as a highly crystalline compound, soluble in non-polar solvents. It was also prepared by first converting the chloride into the hydroxide and then treating the latter with toluene-*p*-sulphonamide (cf. Saunders, *J.*, 1950, 684). An ethereal solution of di-*n*-butyldiethyl-lead when treated with dry hydrogen chloride at 0° gave what appeared to be a mixture of products. It is noteworthy that Calingaert, Soroos, and Shapiro (*J. Amer. Chem. Soc.*, 1940, **62**, 1104) showed

that ethyldimethyl-lead chloride, when heated in acetone, undergoes a redistribution reaction, yielding a random mixture containing all four possible trialkyl-lead chlorides. Such a redistribution may occur slowly in the cold.

With chloroacetic acid, however, some success was obtained. When this was warmed with dibutyldiethyl-lead in ethereal solution, a colourless crystalline compound was formed which appeared to be impure *n*-butyldiethyl-lead chloroacetate, *i.e.*, a heavier group had been replaced by the acid.

The sternutatory action of ethyldipropyl-lead chloride, ethyldipropylplumbitoluene-*p*-sulphonamide, diethylpropyl-lead propionate, diethylpropyl-lead chloroacetate, and *n*-butyldiethyl-lead chloroacetate was powerful, and these compounds were probably slightly superior to tri-*n*-propyl- and tri-*n*-butyl-lead salts, in this respect. Hence they are placed in sternutatory grade 3+.

Experimental.

Diethyl-lead Dibenzoate.—Benzoic acid (5 g.) was heated with tetraethyl-lead (8 c.c.) and a small piece of silica gel on a water-bath for ½ hour. The mass liquefied, then effervesced and finally solidified. The *dibenzoate* recrystallised from benzene as long colourless needles, m. p. 168° (Found: Pb, 40·8. $C_{18}H_{20}O_4Pb$ requires Pb, 40·8%). The same product was obtained without the gel, but longer heating was required (1 hour). The compound was insoluble in water, but soluble in hot alcohol and benzene. When heated slowly it gave the odour of ethyl benzoate and, when heated rapidly, it decomposed with a mild explosion.

A weighed quantity of the dibenzoate (*ca.* 1 g.) was dissolved in dry benzene, and dry hydrogen chloride passed into the solution for a few minutes. The precipitated diethyl-lead dichloride was filtered off, washed with benzene, and dried *in vacuo* (Found: Cl, 21·2. Calc. for $C_4H_{10}Cl_2Pb$: Cl, 21·1%).

Tripropyl-lead Chloroacetate.—Tetrapropyl-lead (3 c.c.), chloroacetic acid (1 g.), and silica gel were heated on a water-bath for ½ hour. The chloroacetate, recrystallised from light petroleum (b. p. 40—60°), had m. p. 109—110° (Found: Pb, 48·3. Calc. for $C_{11}H_{23}O_2ClPb$: Pb, 48·2%), and was identical with the compound obtained by the action of chloroacetic acid on tripropyl-lead hydroxide (Part I, *loc. cit.*).

Diethyl-lead Dichloride.—Tetraethyl-lead (12 c.c.) was dissolved in anhydrous toluene (100 c.c.) in a conical three-necked flask fitted with a reflux condenser (closed by a calcium chloride tube), an inlet tube for hydrogen chloride, and a thermometer dipping into the liquid, and heated to 90°. Dry hydrogen chloride was passed in, and after about 20 minutes a white precipitate began to form. After passage of the gas for a further hour, the solid was filtered off from the hot solution, and washed with boiling toluene (in which the triethyl-lead chloride is soluble). It was dried *in vacuo* over wax and was then pure (16 g., 80%), having m. p. 220° (decomp. leaving an infusible residue). If desired, it could be recrystallised in small quantity from hot water (Found: Cl, 21·1; Pb, 61·9. Calc. for $C_4H_{10}Cl_2Pb$: Cl, 21·1; Pb, 61·6%). Solubility: 2% in water at 15°, 0·1% in boiling alcohol. The aqueous solution of the pure dichloride gave a cream-coloured precipitate with ammonium sulphide. If traces of plumbous chloride were present, the precipitate was black.

Reaction between Diethyl-lead Dichloride and Silver Chloroacetate.—(*a*) Diethyl-lead dichloride (3·36 g.) suspended in ethyl alcohol (40 c.c.), was mixed with silver chloroacetate (4 g.) dissolved in hot water (40 c.c.). The mixture was heated and silver chloride (92% yield) was filtered off. On cooling, the filtrate deposited colourless crystals with a silvery lustre, m. p. *ca.* 179°, and were proved to be lead chloroacetate. The filtrate, on slow evaporation, gave long needles, m. p. and mixed m. p. with authentic specimen of triethyl-lead chloroacetate, 147° (Found: Pb, 53·8. Calc. for $C_8H_{17}O_2ClPb$: Pb, 53·5%).

(*b*) *In the cold.* Silver chloroacetate (5 g.) was ground in a mortar with diethyl-lead dichloride (4 g.) and sufficient water to make a paste, and set aside for an hour. The mixture was filtered, and hydrogen sulphide was passed through the solution to remove traces of lead; the black sulphide was filtered off, and a small portion of the filtrate then gave with hydrogen sulphide a cream-coloured precipitate of $PbEt_2S$. The remainder of the filtrate was evaporated below 25°. Colourless crystals of *diethyl-lead bischloroacetate* were obtained and, recrystallised from absolute alcohol, had m. p. 180° (efferv.) (Found: Pb, 45·8. $C_8H_{14}O_4Cl_2Pb$ requires Pb, 45·8%). An aqueous solution gave a cream-coloured precipitate with hydrogen sulphide, thus showing that no Pb^{++} had been produced during the recrystallisation from alcohol.

Diethyl-lead Dihydroxide and Oxide.—Diethyl-lead dichloride (15 g.) was shaken with ether (75 c.c.) in a separating-funnel together with aqueous sodium hydroxide solution (30%, 50 c.c.). The solid dissolved, and after for 24 hours dense crystals were produced and sank to the bottom of the aqueous layer. These crystals were run off together with the minimum amount of aqueous sodium hydroxide, and were collected in a sintered funnel, washed with a small volume of aqueous acetone (1 : 1 by vol.), and dried on a porous tile. They were purified by dissolving them in the minimum quantity of warm water (40°) and placing the solution in a desiccator over concentrated sulphuric acid. After several days *diethyl-lead dihydroxide hexahydrate* crystallised and was filtered off and dried on a porous tile (Found: Pb, 51·2. $C_4H_{12}O_2Pb,6H_2O$ requires Pb, 50·9%). The hexahydrate formed white transparent needles, readily soluble in cold water, less soluble in alcohol, insoluble in ether, acetone, benzene, and light petroleum. When heated in a capillary tube, it lost water at *ca.* 120°, a brown colour developed at

135°, and above 210° the solid blackened. When it was heated strongly in bulk in a crucible, a mild explosion took place.

Loss of weight determinations. A weighed quantity of the hexahydrate (*ca.* 0·25 g.) was placed in a vacuum-desiccator over concentrated sulphuric acid until no further loss in weight took place (16 hours) [Found: loss, 30·4. $PbEt_2(OH)_2.6H_2O \longrightarrow PbEt_2O$ requires loss, 31·0%]. The residue of *diethyl-lead oxide* contained Pb, 73·7% ($C_4H_{10}OPb$ requires Pb, 73·7%). The oxide was insoluble in water, but dissolved in dilute acetic acid. The loss in weight after long heating at 100° showed that the composition of the residue approximated to PbO.

Conversion of Diethyl-lead Dihydroxide Hexahydrate into the Dichloride.—The hexahydrate (10·5 g.) was dissolved in water and neutralised with dilute hydrochloric acid. The solution was rapidly evaporated to dryness in a vacuum-desiccator and the residue weighed [Found: ratio $PbEt_2Cl_2$: $PbEt_2(OH)_2.6H_2O$, 0·806. Calc.: 0·825]. The chloride content of the residue was determined gravimetrically (Found: Cl, 20·7. Calc. for $PbEt_2Cl_2$: Cl, 21·1. Calc. for $PbEt_2Cl$: Cl, 10·8%).

Diethyl-lead Sulphite.—Tetraethyl-lead (10 c.c., 0·05 mol.) was dissolved in ether (100 c.c.), and water (2 c.c., *ca.* 0·1 mol.) added. Sulphur dioxide was passed in for about 5 hours and a white amorphous powder was precipitated. This was filtered off, and the filtrate returned to the apparatus and again treated with sulphur dioxide until no further precipitation occurred. A further small yield (*ca.* 0·3 g.) of solid could be obtained by keeping the reaction mixture for a further 15 hours. The product was washed with ether and dried *in vacuo* over concentrated sulphuric acid; yield 17 g. (99%). *Diethyl-lead sulphite* was then obtained as an amorphous white powder which did not melt (Found: Pb, 59·8, 60·15. $C_4H_{10}O_3SPb$ requires Pb, 60·0%). The sulphite is insoluble in water, alcohol, and ether, and soluble in dilute acids with evolution of sulphur dioxide. When treated with dilute hydrochloric acid in the cold and kept, it afforded pure crystals of diethyl-lead dichloride.

The above preparation was carried out in a tall cylindrical vessel in order (*a*) to ensure maximum absorption of sulphur dioxide, and (*b*) to avoid loss of tetraethyl-lead by creeping over the sides.

Diethyl-lead Dibenzoate.—Diethyl-lead sulphite (3 g., 50% excess) was heated under reflux for 1½ hours with benzoic acid (1·5 g.) dissolved in alcohol, sulphur dioxide being evolved. The unchanged sulphite was then filtered off, and the filtrate evaporated to dryness. The solid thus obtained was extracted with successive quantities of boiling water (20 c.c.) to remove benzoic acid, and the extract filtered hot each time. The insoluble residue from this treatment had m. p. 168°, and was further purified, if necessary, by recrystallisation from benzene; the yield was nearly theoretical, and the m. p. and mixed m. p. with the product obtained from tetraethyl-lead and benzoic acid, 168°.

Note. In order to show that the hot water extraction used to remove traces of benzoic acid did not promote disproportionation, the product from tetraethyl-lead was subjected to prolonged boiling with water without change of m. p. When it was heated gently in the open, an odour of ethyl benzoate was noted, but on strong heating a mild explosion took place.

Action of Benzoic Acid on Triethyl-lead Hydroxide.—To an aqueous-alcoholic solution of triethyl-lead hydroxide (see Part I, *J.*, 1949, 919) was added a concentrated alcoholic solution of benzoic acid (*ca.* 1·5 g.) until the mixture was acid to litmus; the whole was then made just alkaline by more triethyl-lead hydroxide. The product was poured into cold water, and the precipitate filtered off. The filtrate gave more of the product on evaporation. The crude *triethyl-lead benzoate* recrystallised from light petroleum (b. p. 100—120°) as colourless crystals, m. p. 126° (3·5 g., 80%) (Found: Pb, 49·6. $C_{13}H_{20}O_2Pb$ requires Pb, 49·9%). The compound is very soluble in cold alcohol, acetone, and benzene.

Diethyl-lead Bischloroacetate.—Diethyl-lead sulphite (3·5 g., 0·01 mol.) was treated with a concentrated solution of chloroacetic acid (3·5 g., 0·04 mol., in 5 c.c. of water) and, when effervescence had subsided, the mixture was gently warmed to complete the reaction. It was then filtered, and the filtrate cooled and concentrated in a desiccator containing solid potassium hydroxide. The crystals thus obtained, when filtered off and washed with ether, were pure, having m. p. and mixed m. p. with product from diethyl-lead chloride and silver chloroacetate, 180° (efferv.). A solution of this first crop of crystals in water gave a yellow precipitate with hydrogen sulphide, thus proving the absence of lead chloroacetate.

Later crops of crystals which separated from the concentrated filtrate were less pure and were contaminated with plumbous ions. Purification of these could be effected by recrystallisation from absolute alcohol or by partial precipitation with hydrogen sulphide.

Prolonged boiling during the preparation or during recrystallisation must be avoided as the compound decomposes in these circumstances.

Diethyl-lead Bistrichloroacetate.—Diethyl-lead sulphite (3 g.) was added to a solution of trichloro-acetic acid (5 g., *i.e. ca.* 80% excess) in warm water (5 c.c.). A reaction took place with vigorous evolution of sulphur dioxide. On cooling, the mixture solidified and sufficient hot water was therefore added to dissolve the mass, and the resulting solution was filtered. Crystals were deposited on cooling and were filtered off. Further crops were obtained by concentration of the filtrate *in vacuo* at room temperature, over concentrated sulphuric acid. The combined crops were recrystallised as quickly as possible from hot water, and *diethyl-lead bistrichloroacetate* was obtained in clusters of colourless needles, m. p. 151° (efferv.) (Found: Pb, 34·5. $C_8H_{10}O_4Cl_6Pb$ requires Pb, 35·0%). A freshly prepared aqueous solution gave a clean cream-coloured precipitate with hydrogen sulphide. The aqueous solution, however, after long storage contained plumbous ions, but this decomposition was less rapid than that of the corresponding chloroacetate.

The following two new compounds were prepared similarly to the bischloroacetate. *Diethyl-lead ditoluene-p-sulphonate.* From sulphite (5 g.) and toluene-*p*-sulphonic acid (5 g.) in water (10 c.c.); recrystallised *in vacuo* at room temperature or quickly from warm water; yield 5 g. (60%); highly

crystalline long needles without m. p., but giving a black, then finally white residue (lead sulphate) on heating (Found: Pb, 33·5. $C_{18}H_{34}O_6S_2Pb$ requires Pb, 34·1%); soluble in hot water, slightly soluble in alcohol and benzene. *Diethyl-lead ditoluene-o-sulphonate*; yield 60%; perfect colourless oblique rhombohedra; when heated, it contracted at 165°, and then decomposed to lead sulphide and finally lead sulphate (Found: Pb, 33·3%), slightly soluble in cold water, readily soluble in hot water, much less soluble in alcohol, benzene, and other organic solvents.

Diethyl-lead Bisthiolacetate.—This was prepared in the cold from sulphite (4 g.) and thioacetic acid (2 g., 13% excess). The cold reaction mixture went almost solid, and after filtration was dried *in vacuo*, giving an almost pure product. The *bisthiolacetate* recrystallised from hot benzene or ethyl alcohol in pale yellow rectangular tablets, m. p. 84·5—85° to a pale yellow liquid which then darkened slowly and finally decomposed at 160° (Found: Pb, 49·5. $C_8H_{16}O_2S_2Pb$ requires Pb, 49·9%). The compound decomposed after storage in a sealed tube for some months.

Conversion of the Bisthiolacetate into the Dichloride.—The thiolacetate (1 g.) was dissolved in alcohol, and concentrated hydrochloric acid (5 c.c.) added. The dichloride crystallised, was filtered off, and recrystallised rapidly from hot water (Found: Cl, 21·3. Calc. for $C_4H_{10}Cl_2Pb$: Cl, 21·1%). The chloride when dissolved in water gave a cream-coloured precipitate with ammonium sulphide.

Triethyl-lead Thiolacetate.—Thioacetic acid (1 g.) was dissolved in aqueous alcohol, and an aqueous solution of triethyl-lead hydroxide added until the mixture was alkaline to litmus. An oil separated, but, on addition of more water and vigorous shaking, it solidified. The *thiolacetate* recrystallised from aqueous dioxan as almost white needles, m. p. 45° (Found: Pb, 56·1. $C_8H_{18}OSPb$ requires Pb, 56·1%); it decomposed on storage.

Action of Thioacetic Acid on Tetraethyl-lead.—(i) *In the cold.* Tetraethyl-lead (4 c.c., 0·02 mol.) was mixed with thioacetic acid (1·5 g.), and the solution kept for *ca.* 20 hours at room temperature. A mass of long white needles was deposited; these were filtered off and washed with ether and were then pure. If necessary they could be recrystallised from benzene and had m. p., and mixed m. p. with product from the foregoing preparation, 45°.

(ii) *At* 100°. Tetraethyl-lead (8 c.c., 0·04 mol.) and thioacetic acid (6 g., 0·08 mol.) were heated under reflux on a water-bath for 3 hours, the mixture filtered while hot, and the filtrate kept overnight; a large mass of pale yellow crystals (A) was deposited, as well as other crystals (B) in the form of orange-coloured nodules. These were filtered off, and the filtrate deposited fine yellow needles (C) when kept for 24 hours.

The crystals (A) and (B) were separated mechanically, and (A) was recrystallised from benzene and washed with ether, well-defined, pale yellow, flat tablets being obtained. These were identified as diethyl-lead bisthiolacetate by m. p. and mixed m. p. with authentic specimen obtained from diethyl-lead sulphite. The crystals (B) were identified as plumbous thiolacetate (see below). The needles (C) had m. p. 44·5° and were found to be triethyl-lead thiolacetate, identical with the compound obtained from triethyl-lead hydroxide and thioacetic acid.

(iii) *At* 100° *with silica gel.* Tetraethyl-lead (3·2 g., 0·01 mol.) was heated under reflux on a water-bath with thioacetic acid (1·5 g., 0·02 mol.) and silica gel for 20 minutes. Darkening took place, and the product recrystallised from benzene as dark orange needles (Found: Pb, 58·0. $C_4H_6O_2S_2Pb$ requires Pb, 58·0%). When heated slowly the *plumbous thiolacetate* darkened at 140—165° and then decomposed. On strong heating in air, lead sulphide and lead sulphate were produced. An aqueous solution was converted into lead sulphide by hydrogen sulphide and into lead chloride by hydrochloric acid. The product was further identified as plumbous thiolacetate by comparison with a specimen prepared from lead carbonate and thioacetic acid, followed by recrystallisation from benzene. Recrystallisation from water gave white instead of pale yellow needles.

Disproportionation of Diethyl-lead Bischloroacetate.—It was essential to use absolutely pure diethyl salt, free from plumbous ions, for this investigation. Diethyl-lead dichloride (4 g.) was heated under reflux with water (25 c.c.) for 30 minutes. The reaction mixture was then cooled in ice, and the crystals (A) so obtained were filtered off and washed with cold water. The aqueous filtrate was distilled until about 5 c.c. of liquid remained. This residual liquid on cooling deposited a further crop of (A). Dispersed in the aqueous distillate was an insoluble oil which possessed a powerful odour of ethyl chloroacetate. The aqueous suspension on treatment with potassium iodide and sodium hypochlorite solution, did not give iodoform, showing that ethyl alcohol was not a product of the reaction. The suspension was made alkaline with sodium hydroxide solution and heated under reflux for 15 minutes and distilled, the distillate now giving the iodoform reaction. The alkaline residue was proved to contain sodium chloroacetate.

The solid (A) was dried and extracted with boiling benzene. On cooling, the extract deposited long needles, m. p. 145·5°, proved to be triethyl-lead chloroacetate. The residue, insoluble in benzene, recrystallised from hot water as characteristic pearly leaflets which decomposed gradually on heating with blackening at *ca.* 176°. Its aqueous solution gave a heavy black precipitate with hydrogen sulphide without trace of a cream-coloured precipitate. These properties are characteristic of plumbous chloroacetate.

Disproportionation of Di-n-propyl-lead Diacetate.—Moist silver oxide (5·3 g., containing *ca.* 50% of water) was shaken with an alcoholic suspension of di-*n*-propyl-lead dichloride (3·3 g.). The mixture was filtered, and to the filtrate of the dihydroxide was added dilute acetic acid. No precipitate separated, and the solution was evaporated at 100°. The white residue obtained was dried and extracted with light petroleum (b. p. 40—60°), which on cooling gave white needles (B). The residue after the extraction was recrystallised from alcohol (C).

The substance (B) was twice recrystallised from light petroleum and then had m. p. 126—127° alone and with the *tripropyl-lead acetate* made from acetic acid and tripropyl-lead hydroxide (Found : Pb, 51·9. $C_{11}H_{24}O_2Pb$ requires Pb, 52·4%). The substance (C) had m. p. 195° and was proved to be lead acetate (Found : Pb, 63·2. Calc. for $C_4H_6O_4Pb$: Pb, 63·7%). During the evaporation of the original aqueous-alcoholic solution, an ester was obtained and identified as propyl acetate.

In the above reaction, it was probable that dipropyl-lead diacetate was first produced and then disproportionated to tripropyl-lead acetate and lead acetate. To confirm this, the aqueous-alcoholic solution was allowed to evaporate in a desiccator at room temperature and a solid residue was obtained which was now completely soluble in hot light petroleum (b. p. 40—60°); white needles separated on cooling (Found : Pb, 49·7. Calc. for dipropyl-lead diacetate, $C_{10}H_{20}O_4Pb$: Pb, 50·4%), m. p. 120° (decomp.), mixed m. p. with tripropyl-lead acetate 104—114° (cf. Part I, *loc. cit.*). When the solid diacetate was heated a marked ester-like odour was produced. An aqueous-alcoholic solution of the diacetate was evaporated at 100° and worked up as above. The quantities of tripropyl-lead acetate and lead acetate obtained were in accordance with equation (B) (p. 660), and an odour of ester was also produced.

Diethyldi-n-propyl-lead.—Magnesium (14·4 g.), dry ether (150 c.c.), a crystal of iodine, and a small amount of *n*-propyl bromide were mechanically stirred, and the remainder of the alkyl halide (total amount, 73·8 g.) in ether (150 c.c.) added. At the end of the reaction, diethyl-lead dichloride (50 g., 0·25 mol.) was added in small portions. After the vigorous action had subsided, the mixture was heated on a water-bath for 3 hours, cooled, decomposed with water, extracted with ether, and dried. After distillation of the ether, the residue distilled at 70—72°/4 mm.

Diethylpropyl-lead Chloroacetate.—Diethyldi-*n*-propyl-lead (2·4 g.), dissolved in a small quantity of ether, chloroacetic acid (0·63 g.), and silica gel were heated on a boiling-water bath for 1½ hours. The *chloroacetate* which separated on cooling was recrystallised from a mixture of benzene and light petroleum (b. p. 60—80°) and had m. p. 112° (Found : Pb, 51·4. $C_9H_{19}O_2ClPb$ requires Pb, 51·9%).

Diethylpropyl-lead Propionate.—This was prepared by heating diethyldipropyl-lead (3·5 g.), propionic acid (0·74 g.), and silica gel on a water-bath for 1½ hours. The *propionate* was recrystallised from ethyl acetate, m. p. 86° (Found : Pb, 54·0. $C_{10}H_{22}O_2Pb$ requires Pb, 54·4%).

N-(*Ethyldipropylplumbi*)*toluene*-p-*sulphonamide.*—Ethyldipropyl-lead chloride was first prepared by passing dry hydrogen chloride through a solution of diethyldipropyl-lead (5 c.c.) in dry light petroleum (b. p. 40—60°; 50 c.c.) until saturated. The product was then filtered, and the filtrate concentrated until solid separated. This was partly purified by extracting the solid with alcohol, filtering, and evaporating the filtrate to dryness. The sodio-derivative of toluene-*p*-sulphonamide (1·28 g.) was suspended in alcohol, and the above chloride (2·1 g.) dissolved in alcohol was added and the mixture heated under reflux for 20 minutes, filtered, and water added to the filtrate. The N-(*ethyldipropylplumbi*)*toluene*-p-*sulphonamide*, separated and recrystallised from benzene–light petroleum (b. p. 40—60°), had m. p. 94·5° (Found : C, 36·6; H, 5·7; Pb, 41·7. $C_6H_4Me{\cdot}SO_2{\cdot}NH{\cdot}PbEtPr_2$ requires C, 36·6; H, 5·5; Pb, 42·1. $C_6H_4Me{\cdot}SO_2{\cdot}NH{\cdot}PbEt_2Pr$ requires C, 35·1; H, 5·2; Pb, 43·3%).

Alternative preparation. The chloride (2·4 g.), dissolved in alcohol, was shaken for 10 minutes with moist silver oxide (2·8 g.), and the silver chloride filtered off. To the filtrate an alcoholic solution of toluene-*p*-sulphonamide was added, and after 10 minutes, water was added. The plumbisulphonamide thus obtained and recrystallised as above had m. p. 94·5° (Found : Pb, 42·1%).

n-*Butyldiethyl-lead Chloroacetate* (impure).—Dibutyldiethyl-lead was prepared according to Jones, Evans, Gulwell, and Griffiths (*J.*, 1935, 41). The plumbane (1·9 g., 0·005 mol.) was added to chloroacetic acid (0·6 g., 0·006 mol.) dissolved in absolute ether (5 c.c.), and the solution heated, with a few pieces of porous pot as catalyst, under reflux for 15 minutes on the water-bath. On addition of excess of water, a white precipitate was formed; this was filtered off, and the chloroacetate recrystallised from a small volume of light petroleum (b. p. 60—80°); m. p. 82—83° (Found : C, 29·9; H, 5·1; Pb, 48·6. $C_{10}H_{21}O_2ClPb$ requires C, 28·9; H, 5·1; Pb, 49·8%) [other possibilities are : $PbEt_2(O{\cdot}CO{\cdot}CH_2Cl)_2$ requires C, 21·2; H, 3·1; Pb, 45·9%. $PbEtBu_2(O{\cdot}CO{\cdot}CH_2Cl)$ requires C, 32·5; H, 5·7; Pb, 46·7%. $PbBu_2(O{\cdot}CO{\cdot}CH_2Cl)_2$ requires C, 28·3; H, 4·35; Pb, 40·8%].

We thank Dr. G. W. Kenner and Messrs. H. Booth and T. S. Worthy with whom we have had valuable discussions about the mechanism of disproportionation.

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142. *Organic Fluoro-compounds. Part IV. The Hoesch Reaction with Trifluoromethyl and Trichloromethyl Cyanides.*

By W. B. Whalley.

By the Hoesch reaction with trifluoromethyl cyanide, resorcinol, 2- and 4-ethylresorcinol, phloroglucinol mono- and tri-methyl ethers, 4-hydroxyveratrole, and 6-methoxy-3-methylcoumarone give the corresponding ω-trifluoromethyl ketones. These, although moderately stable to alkali, ultimately undergo the haloform reaction.

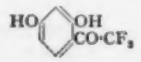
Trichloromethyl cyanide furnished the corresponding ω-trichloroacetophenones from a more restricted range of phenols, but the reaction proceeded readily with hydroxy- and methoxy-coumarones and phloroglucinol monomethyl ether. These derivatives are very easily hydrolysed to the corresponding acids, and in particular provide an alternative route to certain 2-carboxycoumarones and an approach to the hitherto inaccessible 2 : 4-dihydroxy-6-methoxybenzoic acid (XII; R = OH). Conditions are detailed for the direct conversion of the ω-trichloroacetophenones into the corresponding methyl esters and for the rapid reduction of the trichloroacetyl group to the ethyl group. A Gattermann aldehyde synthesis, using ω-trichloro-2 : 4-dihydroxy-6-methoxyacetophenone (VII; R = H), and subsequent hydrolysis of the 3-formyl derivative readily provides the difficultly accessible 2 : 6-dihydroxy-4-methoxybenzaldehyde.

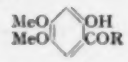
Theoretical considerations appear to indicate that ω-trifluoroacetophenones should undergo the haloform reaction with the production of the corresponding acid and fluoroform, and indeed, one example (ω-trifluoroacetophenone) is quoted by Simons and Ramler (*J. Amer. Chem. Soc.*, **1943**, **65**, 389). With the object of using the *C*-trifluoroacetyl group as a protecting group (easily removable by conversion into the acid and subsequent decarboxylation) for reactive positions in phenols and particularly in phloroglucinol, an investigation of the preparation of such ketones by the Hoesch synthesis was initiated. The literature (cf., *inter alia*, Houben, *Ber.*, 1926, **59**, 5880) appeared to indicate that ω-trichlorohydroxyacetophenones are not generally available, because trichloromethyl cyanide reacts with phenols with the preferential production of the corresponding phenyl trichloroacetimidate hydrochlorides rather than the ketones; and it seemed that trifluoromethyl cyanide, which has not been previously employed in the Hoesch ketone synthesis, might be more useful. However, the trifluoromethyl ketones were found to be more stable than had been expected and consequently the behaviour of trichloromethyl cyanide in the Hoesch condensation was re-examined.

The production of the corresponding ω-trifluoroacetophenones from a number of phenols and trifluoromethyl cyanide proceeded normally,* furnishing the ketones in high yield and necessitating only slight alterations in the usual experimental conditions occasioned by the low boiling point of the cyanide (see Experimental). Resorcinol gave ω-trifluoro-2 : 4-dihydroxyacetophenone (I), readily methylated with methyl iodide–potassium carbonate and then hydrolysed by alkali to 2 : 4-dimethoxybenzoic acid, thus establishing the orientation of (I). 2- and 4-Ethylresorcinol behaved similarly, giving 2-ethyl- (IV; R = Et, R′ = H) and 5-ethyl-ω-trifluoro-2 : 4-dihydroxyacetophenone (IV; R = H, R′ = Et) respectively. 4-Hydroxyveratrole and phloroglucinol monomethyl ether furnished ω-trifluoro-2-hydroxy-4 : 5-dimethoxy- (II; R = CF_3) and ω-trifluoro-2 : 4-dihydroxy-6-methoxyacetophenone (III; R = H) respectively. The rather vigorous conditions necessary to hydrolyse (III; R = H) caused simultaneous decarboxylation of the acid moiety and the orientation of the ketone is assumed by analogy with that of the corresponding ω-trichlorophloroacetophenone (VII; R = H) and the known behaviour of phloroglucinol monomethyl ether under the conditions of the Hoesch synthesis. Methylation of (III; R = H) gave ω-trifluoro-2 : 4 : 6-trimethoxyacetophenone (VI; R = CF_3) identical with a specimen prepared by the interaction of phloroglucinol trimethyl ether and trifluoromethyl cyanide. Phloroglucinol, orcinol, and pyrogallol all failed to react with trifluoromethyl cyanide.

* Despite this normal behaviour in the Hoesch reaction attempts to prepare trifluoroacetaldehyde from trifluoromethyl cyanide by Stephen's reaction were unsuccessful. This is in agreement with Henne, Pelley, and Alm's findings (*J. Amer. Chem. Soc.*, 1950, **72**, 3370) which became available after the completion of this manuscript.

These ω-trifluoroacetophenones did not furnish 2 : 4-dinitrophenylhydrazones under the usual conditions and were rather surprisingly stable to the action of alkali, but under moderately vigorous conditions underwent fission to give a gas (presumably fluoroform) and the


(I.)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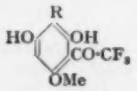
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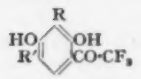
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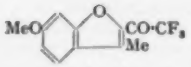
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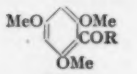
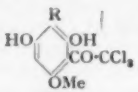

(VI.)

corresponding acid, usually in low yield because of partial decarboxylation. Methylation with methyl iodide–potassium carbonate proceeded normally and fully; attempted Clemmensen reduction caused rapid resinification, presumably owing to the action of the liberated hydrofluoric acid. The strong electron affinity of the trifluoroacetyl group is illustrated by the ease of dissolution of all these ω-trifluorohydroxyacetophenones in sodium hydrogen carbonate solution.

ω-Trifluoro-2 : 4-dihydroxy-6-methoxyacetophenone (III; R = H), readily underwent the Gattermann reaction to give ω-trifluoro-3-formyl-2 : 4-dihydroxy-6-methoxyacetophenone (III; R = CHO), the orientation of which is inferred by analogy with the corresponding trichloro-compound (VII; R = CHO).

The Hoesch synthesis with 6-methoxy-3-methylcoumarone and trifluoromethyl cyanide gave, with remarkable facility and in high yield the trifluoromethyl ketone (V) converted by alkaline hydrolysis into 6-methoxy-3-methylcoumarone-2-carboxylic acid (XI; R = Me; R′ = OH).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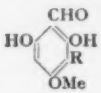
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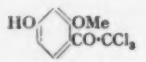
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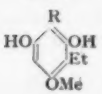
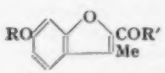
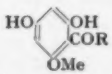

(X.)


(XI.)


(XII.)

Turning then to trichloromethyl cyanide, we found the Hoesch synthesis to fail completely with phloroglucinol, resorcinol, orcinol, and pyrogallol, but to proceed readily with phloroglucinol monomethyl ether, giving (VII; R = H). By the Gattermann synthesis this yielded ω-trichloro-3-formyl-2 : 4-dihydroxy-6-methoxyacetophenone (VII; R = CHO) in good yield. The compounds (VII; R = H = CHO) readily dissolved in warm 2N-sodium hydrogen carbonate with the evolution of chloroform (cf. Houben and Fischer, *J. pr. Chem.*, 1929, [ii], **123**, 313) and the production of 2 : 4-dihydroxy-6-methoxybenzoic acid (XII; R = OH) and its 3-formyl derivative (VIII; R = CO_2H) respectively. Esterifying the former acid with diazomethane or warming (VII; R = H) with methyl alcohol containing a trace of potassium hydroxide readily gave methyl 2 : 4-dihydroxy-6-methoxybenzoate (XII; R = OMe). When an aqueous solution of (VIII; R = CO_2H) was gently refluxed for 5 minutes in an atmosphere of nitrogen, quantitative conversion into 2 : 6-dihydroxy-4-methoxybenzaldehyde (VIII; R = H) occurred, thus providing a much superior route to this difficultly accessible substance (Karrer and Bloch, *Helv. Chim. Acta*, 1927, **10**, 378; Karrer, Lichtenstein, and Helfenstein, *ibid.*, 1929, **12**, 991). The non-identity of the ester (XII; R = OMe) with methyl 2 : 6-dihydroxy-4-methoxybenzoate and the production of 2 : 6-dihydroxy-4-methoxybenzaldehyde (VIII; R = H) from (VII; R = CHO) clearly established the orientation of the acid (XII; R = OH), the parent ω-trichloroacetophenone (VII; R = H), and the aldehyde (VII; R = CHO). Methyl 2 : 4-dihydroxy-6-methoxybenzoate (XII; R = OMe) gave rise by the

Gattermann method to the aldehydo-ester (VIII; R = CO_2Me) which on hydrolysis furnished (VIII; R = H) in low yield, thus affording additional evidence for the orientation previously adduced for (XII; R = OH), (XII; R = OMe), and (VII; R = H).

Clemmensen reduction converted the ω-trichloroacetophenones (VII; R = H) and (VII; R = CHO) readily almost quantitatively into 1-ethyl-2 : 4-dihydroxy-6-methoxybenzene (X; R = H) and 3-ethyl-2 : 6-dihydroxy-4-methoxytoluene (X; R = Me). The Clemmensen reduction of α-halogeno-ketones appears to have been reported in only two instances (Johnson and Hodge, *J. Amer. Chem. Soc.*, 1913, **35**, 1014, and Funke and Ristic, *J. pr. Chem.*, 1936, **146**, 151) where the $-CO\cdot CH_2Cl$ group was reduced to an ethyl group.

In contrast to the behaviour of the corresponding ω-trifluoroacetophenones, attempted methylation of (VII; R = H) by methyl iodide–potassium carbonate removed the trichloromethyl residue with quantitative formation of methyl 2 : 4 : 6-trimethoxybenzoate (VI; R = OMe). ω-Trichloro-2 : 4 : 6-trimethoxyacetophenone (VI; R = CCl_3) was formed directly by the Hoesch condensation of trichloromethyl cyanide and phloroglucinol trimethyl ether, and on Clemmensen reduction readily furnished 1-ethyl-2 : 4 : 6-trimethoxybenzene.

Resorcinol monomethyl ether and trichloromethyl cyanide gave ω-trichloro-4-hydroxy-2-methoxyacetophenone (IX) in good yield, together with a very small amount of the isomeric 2-hydroxy-4-methoxy-compound; (IX) was hydrolysed by alkali to 4-hydroxy-2-methoxybenzoic acid. Similarly, 4-hydroxyveratrole and trichloromethyl cyanide readily gave ω-trichloro-2-hydroxy-4 : 5-dimethoxyacetophenone (II; R = CCl_3) which furnished 2-hydroxy-4 : 5-dimethoxybenzoic acid on gentle hydrolysis and was readily converted into methyl 2-hydroxy-4 : 5-dimethoxybenzoate by warm methanol containing a trace of potassium hydroxide.

6-Hydroxy- (Karrer and Widmer, *Helv. Chim. Acta*, 1919, **2**, 454) and 6-methoxy-3-methylcoumarone (Foster, Robertson, and Healey, *J.*, 1939, 1597) readily gave 6-hydroxy- and 6-methoxy-3-methyl-2-trichloroacetylcoumarone (XI; R = H, R′ = CCl_3; R = Me, R = CCl_3) respectively, the orientations being established by alkaline hydrolysis to the corresponding acids. The entry of the trifluoroacetyl and trichloroacetyl groups into the α-position of a hydroxy- or methoxy-3-methylbenzofuran nucleus is in accordance with recent work by Mackenzie and Robertson, (*J.*, 1949, 2057) and affords additional confirmation of the behaviour of this nucleus in the Hoesch condensation (contrast Karrer *et al.*, *Helv. Chim. Acta*, 1919, **2**, 454; 1921, **4**, 718).

Methylation by the methyl iodide–potassium carbonate method of (XI; R = H, R′ = CCl_3), as in the previously described instance of (VII; R = H), took place with the concomitant replacement of the trichloromethyl group by the methoxyl group and the production of methyl 6-methoxy-3-methylcoumarone-2-carboxylate (XI; R = Me, R′ = OMe). 2-Trichloroacetyl-6-methoxy-3-methylcoumarone (XI; R = Me, R′ = CCl_3) was readily converted, in high yield, into the methyl and the ethyl ester (XI; R = Me, R′ = OMe or OEt) respectively when warmed with the appropriate alcohol containing 1 drop of 60% potassium hydroxide solution. Conversion of the trichloroacetyl group into the carbomethoxy-residue under these conditions succeeded in all the cases examined, but attempts to produce the ethyl esters in a similar manner very frequently gave only the corresponding acid; the trifluoromethyl ketones always furnished quantitative yields of the corresponding acids with either alcohol and could not be converted directly into either ester (cf. Houben and Fischer, *Ber.*, 1931, **64**, 2636).

The rapid conversion of the trichloroacetyl group into the ethyl, carboxy-, and carbomethoxy-group provides a useful method, in the limited number of instances where the appropriate ω-trichloroacetophenones are available, for the preparation of *C*-ethyl-phenols, -acids, and -methyl esters.

Experimental.

All the trifluoromethyl ketones described below retained traces of water very tenaciously, and after purification by crystallisation specimens for analysis were sublimed in a high vacuum, whereafter satisfactory analytical results were obtained.

ω-Trifluororesacetophenone (I; R = H).—A solution of resorcinol (4 g.) in ether (125 ml.) containing powdered zinc chloride (3 g.) was saturated at about −5° with hydrogen chloride, and trifluoromethyl cyanide (12 g.) (prepared from trifluoroacetamide and phosphoric oxide) was then passed into the mixture. An almost colourless crystalline mass rapidly separated, and after 24 hours at 0° the complex was separated, washed with more ether, and dissolved in water (40 ml.) and the solution heated on the steam-bath for 15 minutes. The red oil which separated did not readily solidify and was taken up in ether, the extract dried and evaporated, and the residue repeatedly extracted with warm light petroleum, giving *ω-trifluororesacetophenone* (4·7 g.) in long, slender, colourless needles, m. p. 103° (Found: C, 46·2; H, 3·0; F, 27·6. $C_8H_5O_3F_3$ requires C, 46·6; H, 2·4; F, 27·7%). The ketone does not give

a 2 : 4-dinitrophenylhydrazone under the usual conditions, and is readily soluble in ether, acetone, benzene, and alcohol, and moderately soluble in petroleum, and the alcoholic solution exhibits a strong red-brown ferric reaction. The compound is very sparingly soluble in hot water, but dissolves readily in cold 2N-sodium hydrogen carbonate and 2N-sodium hydroxide from which it is precipitated substantially unchanged by acids 8 hours later.

Methylation of this ketone (1 g.) in boiling acetone (75 ml.) containing potassium carbonate (4 g.) and methyl iodide (5 ml.) during 5 hours furnished the *dimethyl ether* (1 g.) in massive, colourless prisms, m. p. 52°, from light petroleum (Found: C, 50·6; H, 3·5; F, 23·4. $C_{10}H_9O_3F_3$ requires C, 51·3; H, 3·8; F, 24·4%). The substance is insoluble in cold 2N-sodium hydrogen carbonate and 2N-sodium hydroxide, but when heated for 15 minutes on the steam-bath with 15% potassium hydroxide solution dissolves rapidly to give an almost colourless solution, with the brisk evolution of fluoroform. Acidification of the solution gave 2 : 4-dimethoxybenzoic acid, identical with an authentic specimen. The dimethyl ether gives no ferric reaction in alcohol, does not furnish a 2 : 4-dinitrophenylhydrazone, and is very soluble in acetone, alcohol, benzene, and ether, and moderately soluble in light petroleum.

3-*Ethyl*-ω-*trifluoro*-2 : 4-*dihydroxyacetophenone* (IV; R = Et, R′ = H).—A solution of 2-ethylresorcinol (2 g.) in ether (100 ml.) containing zinc chloride (2 g.) was saturated at 0° with hydrogen chloride, and trifluoromethyl cyanide (7 g.) passed into the mixture, whereupon a crystalline, almost colourless ketimine salt rapidly separated. After 24 hours at 0° the solid was separated, washed with ether, and dissolved in water (40 ml.), and the solution heated on the steam-bath during 15 minutes, the ketone then separating. Crystallisation from light petroleum gave *3-ethyl-ω-trifluoro*-2 : 4-*dihydroxyacetophenone* in shimmering colourless leaflets (2·5 g.), m. p. 139° (Found: C, 51·0; H, 3·5; F, 24·8. $C_{10}H_9O_3F_3$ requires C, 51·3; H, 3·8; F, 24·4%). The ketone is readily soluble in ether, acetone, alcohol, and benzene, slowly soluble in cold 2N-sodium hydrogen carbonate, gives no 2 : 4-dinitrophenylhydrazone under the usual conditions, exhibits a strong red-brown ferric reaction in alcohol, and is precipitated unchanged after 6 hours when dissolved in 2N-sodium hydroxide.

Methylation in boiling acetone, with potassium carbonate–methyl iodide, furnished 3-ethyl-ω-trifluoro-2 : 4-dimethoxyacetophenone as a colourless oil which on hydrolysis on the steam-bath during 15 minutes with 15% potassium hydroxide solution gave a quantitative yield of 3-ethyl-2 : 4-dimethoxybenzoic acid, m. p. 128°. Sprenger and Ruoff (*J. Org. Chem.*, 1946, **11**, 189) record m. p. 128—129°.

5-*Ethyl*-ω-*trifluoro*-2 : 4-*dihydroxyacetophenone* (IV; R = H; R′ = Et).—4-Ethylresorcinol (2 g.), treated as in the foregoing case, gave the *ketone* (2·4 g.) as long, slender needles, m. p. 99° (from light petroleum) (Found: C, 51·6; H, 4·0; F, 24·9%), having the same properties as its 3-ethyl isomer.

Methylation gave the *dimethyl ether*, which formed slender, glistening prisms (from aqueous methanol), m. p. 65° (Found: C, 54·3; H, 5·6; F, 21·3. $C_{12}H_{13}O_3F_3$ requires C, 55·0; H, 5·0; F, 21·7%). This ketone gave a negative ferric reaction in alcohol, and no 2 : 4-dinitrophenylhydrazone, was soluble in all the usual organic solvents, and was hydrolysed on the steam-bath during 15 minutes with 15% potassium hydroxide solution to 5-ethyl-2 : 4-dimethoxybenzoic acid, m. p. 130°. Desai and Hamid (*Proc. Indian Acad. Sci.*, 1937, **6a**, 287) record m. p. 126°.

ω-*Trifluoro*-2 : 4-*dihydroxy*-6-*methoxyacetophenone* (III; R = H).—Under the above conditions phloroglucinol monomethyl ether (4 g.) and trifluoromethyl cyanide (12 g.) yielded *ω-trifluoro*-2 : 4-*dihydroxy*-6-*methoxyacetophenone*, which separated from benzene in glistening pale yellow plates (2·2 g.), m. p. 154° (Found: C, 45·9; H, 2·7; F, 24·6. $C_9H_7O_4F_3$ requires C, 45·8; H, 3·0; F, 24·2%). This ketone does not furnish a 2 : 4-dinitrophenylhydrazone under the usual conditions, exhibits a strong red-brown ferric reaction in alcohol, is easily soluble in alcohol, acetone, ether, and ethyl acetate, moderately soluble in benzene, and less soluble in light petroleum, and dissolves readily in cold 2N-sodium hydrogen carbonate and 2N-sodium hydroxide, from which it is precipitated by acids, substantially unchanged, after 6 hours.

ω-*Trifluoro*-3-*formyl*-2 : 4-*dihydroxy*-6-*methoxyacetophenone* (III; R = CHO).—When a solution of ω-trifluoro-2 : 4-dihydroxy-6-methoxyacetophenone (III; R = H) (1 g.) in ether (75 ml.) containing zinc cyanide (0·5 g.) and hydrogen cyanide (4 ml.) was saturated at 0° with hydrogen chloride, the coloured crystalline aldimine salt rapidly separated. 24 Hours later the complex was dissolved in water (50 ml.) and heated on the steam-bath during 24 minutes. The *aldehyde* separated from the cooled hydrolysate in reddish-brown crystals, purified by crystallisation from aqueous methanol (charcoal) or by vacuum sublimation (140°/0·1 mm.), to give almost colourless prisms (0·3 g.), m. p. 129°, exhibiting a red-brown ferric reaction in alcohol and very soluble in alcohol (Found: C, 45·8; H, 3·0. $C_{10}H_7O_5F_3$ requires C, 45·5; H, 2·7%). The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in orange-yellow needles, m. p. 278° (decomp.) (Found: N, 12·8. $C_{16}H_{11}O_8N_4F_3$ requires N, 12·6%).

All attempts to remove the $-CF_3$ group by alkaline hydrolysis using a wide variety of conditions were unsuccessful, the rather vigorous conditions required causing resinification.

ω-*Trifluoro*-2 : 4 : 6-*trimethoxyacetophenone* (VI; R = CF_3).—(*a*) Methylation of ω-trifluoro-2 : 4-dihydroxy-6-methoxyacetophenone in boiling acetone by potassium carbonate–methyl sulphate during 6 hours gave a quantitative yield of ω-trifluoro-2 : 4 : 6-trimethoxyacetophenone in shimmering, colourless, slender plates (from aquous methanol), m. p. 60°, identical with a specimen prepared by method (*b*).

(*b*) When a solution of phloroglucinol trimethyl ether (1 g.) in ether (50 ml.) containing zinc chloride (1 g.) was saturated at 0° with hydrogen chloride, followed by trifluoromethyl cyanide (3·5 g.), the ketimine salt rapidly separated in yellow prisms. 24 Hours later the product was hydrolysed with water (50 ml.) during 15 minutes on the steam-bath. The oil which separated solidified on cooling and on crystallisation from aqueous alcohol or, more conveniently, distillation at 100°/0·1 mm., gave the *ketone* (1·7 g.) which had the usual properties of the class; it had m. p. and mixed m. p. 60°, with a

specimen prepared by method (*a*), and mixed with methyl 2 : 4 : 6-trimethoxybenzoate had m. p. *ca.* 40° (Found : C, 50·0; H, 4·5; F, 21·3. $C_{11}H_{11}O_4F_3$ requires C, 50·0; H, 4·2; F, 21·6%).

ω-Trifluoro-2-hydroxy-4 : 5-dimethoxyacetophenone (II; R = CF_3).—4-Hydroxyveratrole (3 g.) in ether (100 ml.) similarly gave this *ketone* which separated from light petroleum in stout, pale yellow-green prisms (3 g.), m. p. 82° (Found : C, 47·5; H, 3·8; F, 23·3. $C_{10}H_9O_4F_3$ requires C, 48·0; H, 3·6; F, 22·8%), readily soluble in the usual organic solvents, slowly soluble in 2N-sodium hydrogen carbonate, giving an olive-green ferric reaction in alcohol and no 2 : 4-dinitrophenylhydrazone. Hydrolysis during 10 minutes on the steam-bath with 2N-sodium hydroxide furnished 2-hydroxy-4 : 5-dimethoxybenzoic acid, identical with an authentic specimen (Head and Robertson, *J.*, 1931, 2432).

2-Trifluoroacetyl-6-methoxy-3-methylcoumarone (V).—This *coumarone* was obtained from 6-methoxy-3-methylcoumarone (Kostanecki and Tambor, *Ber.*, 1909, **42**, 901) (2 g.) under our usual conditions and formed, from aqueous methanol, very pale yellow, stout, massive prisms (3 g.), m. p. 87°, unchanged by sublimation at 100°/0·1 mm. (Found : C, 56·0; H, 3·5; F, 22·2. $C_{12}H_9O_3F_3$ requires C, 55·8; H, 3·5; F, 22·1%). Its properties resembled those of its analogues and it was rapidly hydrolysed by 2N-sodium hydroxide to the 2-carboxylic acid (100%), m. p. and mixed m. p. 190° (decomp.), identical with an authentic specimen (Foster, Robertson, and Healey, *J.*, 1939, 1597).

ω-Trichloro-2 : 4-dihydroxy-6-methoxyacetophenone (VII; R = H).—A solution of phloroglucinol monomethyl ether (5 g.) in ether (70 ml.), containing powdered zinc chloride (4 g.) and trichloromethyl cyanide (10 g.), was saturated at 0° with hydrogen chloride. 24 Hours later the colourless crystalline precipitate was separated, washed with ether, and hydrolysed as above. The product separated as an oil which crystallised. *ω-Trichloro-2 : 4-dihydroxy-6-methoxyacetophenone* (4—5 g.) separated from benzene in almost colourless needles, or from aqueous methanol in glittering pale cream prisms, m. p. 152° (Found : C, 37·7; H, 2·6; Cl, 35·1. $C_9H_7O_4Cl_3$ requires C, 37·9; H, 2·5; Cl, 37·4%). It affords no 2 : 4-dinitrophenylhydrazone under the usual conditions, is readily soluble in acetone, ether, and alcohol, and the alcoholic solution gives a weak red-brown colour with ferric chloride.

1-Ethyl-2 : 4-dihydroxy-6-methoxybenzene (X; R = H).—(*a*) 2 : 4-Dihydroxy-6-methoxyacetophenone (1 g.) in methanol (20 ml.) was added to zinc amalgam (10 g.), concentrated hydrochloric acid (20 ml.), and water (10 ml.), and the mixture refluxed until a test portion exhibited a negative ferric reaction in alcohol (4 hours). The cooled mixture was diluted with water (100 ml.) and extracted with ether (3 × 75 ml.). Evaporation of the washed, dried extract and crystallisation of the residue from benzene–light petroleum gave *1-ethyl-2 : 4-dihydroxy-6-methoxybenzene* (0·6 g.) as glistening, colourless plates, m. p. 109°, exhibiting a negative ferric reaction in alcohol (Found : C, 64·2; H, 7·2. $C_9H_{12}O_3$ requires C, 64·3; H, 7·2%). The *di-p-nitrobenzoate* separated from much alcohol or aqueous acetic acid in pale cream-coloured needles, m. p. 164° (Found : N, 6·3. $C_{23}H_{16}O_9N_2$ requires N, 6·0%).

(*b*) ω-Trichloro-2 : 4-dihydroxy-6-methoxyacetophenone (0·9 g.) was similarly reduced (5 minutes' refluxing) to the same substance (0·3 g.), colourless plates (from light petroleum), m. p. 109°, identical with an authentic specimen. The di-*p*-nitrobenzoate, m. p. 164°, was identical with the previous specimen.

Methyl 2 : 4-Dihydroxy-6-methoxybenzoate (XII; R = OMe).—(*a*) ω-Trichloro-2 : 4-dihydroxy-6-methoxyacetophenone (2 g.) was dissolved in 2N-sodium hydroxide (12 ml.) with cooling. An odour of chloroform became apparent immediately, and 30 minutes later the solution was acidified with 2N-hydrochloric acid and the precipitate collected and crystallised rapidly from aqueous methanol (charcoal), giving 2 : 4-*dihydroxy-6-methoxybenzoic acid* in almost colourless, squat prisms (1·1 g.), m. p. 200° (decomp.) (Found : C, 51·9; H, 4·4. $C_8H_8O_5$ requires C, 52·2; H, 4·3%). The acid is readily soluble in cold 2N-sodium hydrogen carbonate and gives a deep red-brown ferric reaction in alcohol. A suspension of the acid (1·7 g.) in chloroform (10 ml.), treated with ethereal diazomethane, rapidly clarified; the resultant solution was washed with 2N-sodium hydrogen carbonate (25 ml.), dried, and evaporated, giving an almost quantitative yield of *methyl* ester in colourless prisms (from aqueous methanol) or colourless clusters of feathery needles (from benzene), m. p. 194° (Found : C, 54·4; H, 5·0. $C_9H_{10}O_5$ requires C, 54·5; H, 5·1%). The ester gave a deep red-brown ferric reaction in alcohol and was sparingly soluble in ether and chloroform and easily soluble in methanol and ethanol.

(*b*) When ω-trichloro-2 : 4-dihydroxy-6-methoxyacetophenone (0·5 g.) in methanol (10 ml.) containing 60% potassium hydroxide (1 drop) was heated under reflux during 5 minutes, and the solution cooled, acidified with hydrochloric acid, diluted with water, and made alkaline with 2N-sodium hydrogen carbonate, the methyl ester (0·35 g.) was obtained, having m. p. and mixed m. p. 194° and identical with the specimen prepared by method (*a*). Attempts to prepare the ethyl ester in this manner were unsuccessful.

Methyl 3-Formyl-2 : 4-dihydroxy-6-methoxybenzoate (VIII; R = CO_2Me).—The foregoing ester (0·8 g.) in ether (150 ml.) containing zinc cyanide (0·5 g.) and hydrogen cyanide (5 ml.) was saturated at 5° with hydrogen chloride. 24 Hours later the colourless crystalline precipitate was separated, washed with ether, dissolved in water (75 ml.), and the solution rapidly heated to boiling. *Methyl 3-formyl-2 : 4-dihydroxy-6-methoxybenzoate* (0·7 g.) separated from the cooled hydrolysate and crystallised from much methanol in colourless slender prisms, m. p. 184° (Found : C, 53·2; H, 4·6. $C_{10}H_{10}O_6$ requires C, 53·1; H, 4·5%). The aldehyde gave a deep red-brown colour with alcoholic ferric chloride, and the 2 : 4-*dinitrophenylhydrazone* separated from much acetic acid in brick-red, slender prisms, m. p. 299° (decomp.) (Found : N, 13·6. $C_{14}H_{14}O_9N_4$ requires N, 13·8%).

2 : 6-Dihydroxy-4-methoxybenzaldehyde (VIII; R = H).—(*a*) When the preceding aldehydo-ester (0·5 g.) was refluxed in an atmosphere of nitrogen during 45 minutes with 2N-sodium hydroxide (5 ml.) the solution became deep red. After acidification and purification by vacuum-sublimation a small yield of 2 : 6-dihydroxy-4-methoxybenzaldehyde was obtained.

(*b*) A solution of ω-trichloro-2 : 4-dihydroxy-6-methoxyacetophenone (1·5 g.) in ether (100 ml.) containing zinc cyanide (1 g.) and hydrogen cyanide (5 ml.) was saturated with hydrogen chloride at 0° and 24 hours later the colourless crystalline precipitate was collected and hydrolysed. *ω-Trichloro-3-formyl-2 : 4-dihydroxy-6-methoxyacetophenone* crystallised from benzene in massive, almost colourless prisms (1·2 g.), m. p. 150° (Found : C, 38·3; H, 2·2; Cl, 34·0. $C_{10}H_7O_5Cl_3$ requires C, 38·3; H, 2·2; Cl, 34·0%). It exhibited a red-brown ferric reaction in alcohol and the *2 : 4-dinitrophenylhydrazone* separated from aqueous alcohol in rosettes of bright crimson needles, m. p. 247° (decomp.) (Found : N, 12·0. $C_{16}H_{11}O_8N_4Cl_3$ requires N, 11·3%). This aldehydo-ketone (2 g.) was warmed gently with 2N-sodium hydrogen carbonate (20 ml.) until a clear solution was obtained (*ca.* 3 minutes). The cooled solution was acidified with 2N-hydrochloric acid, and the product crystallised from aqueous methanol, giving almost colourless needles of *2 : 4-dihydroxy-3-formyl-6-methoxybenzoic acid* (*ca.* 100%), m. p. 185° (decomp.), exhibiting a deep red-brown ferric reaction in alcohol (Found : C, 50·8; H, 3·7. $C_9H_8O_6$ requires C, 50·9; H, 3·8%).

A mixture of the acid (0·9 g.) and water (15 ml.) containing a few drops of methanol was refluxed in an atmosphere of nitrogen during 15 minutes to give a clear solution. On cooling 2 : 6-dihydroxy-4-methoxybenzaldehyde (0·65 g.) separated in almost colourless needles, m. p. 141—142° (Found : C, 57·2; H, 4·8. Calc. for $C_8H_8O_4$: C, 57·1; H, 4·8%) (Karrer and Bloch, *loc. cit.*, record m. p. 139—140°).

3-Ethyl-2 : 6-dihydroxy-4-methoxytoluene (X; R = Me).—A solution of ω-trichloro-3-formyl-2 : 4-dihydroxy-6-methoxyacetophenone (0·5 g.) in methanol (10 ml.) was added in one portion to concentrated hydrochloric acid (10 ml.), water (5 ml.), and amalgamated zinc (5 g.), and the mixture refluxed until a portion gave no precipitate with aqueous 2 : 4-dinitrophenylhydrazine sulphate solution (10 minutes). The cooled mixture was extracted with ether (4 × 25 ml.), and the dried extracts were evaporated, giving *3-ethyl-2 : 6-dihydroxy-4-methoxytoluene* (0·3 g.) which separated from benzene–light petroleum in clusters of colourless prisms, m. p. 112°, unchanged by sublimation (140°/0·1 mm.), and having no ferric reaction in alcohol (Found : C, 65·9; H, 7·8. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·7%). The *di-p-nitrobenzoate* separated from methanol in very pale greenish-yellow needles, m. p. 178° (Found : N, 6·4. $C_{24}H_{20}O_9N_2$ requires N, 5·8%).

ω-Trichloro-2 : 4 : 6-trimethoxyacetophenone (VI; R = CCl_3).—A solution of phloroglucinol trimethyl ether (5 g.) in ether (100 ml.) containing zinc chloride (5 g.) and trichloromethyl cyanide (10 g.) was saturated at 0° with hydrogen chloride. The ketimine salt was hydrolysed in the usual way. The *product* (3·5 g.) crystallised from aqueous methanol in colourless, long, slender needles, or from benzene–light petroleum in stout, massive, colourless prisms, m. p. 116° (Found : C, 42·3; H, 3·5; Cl, 33·7. $C_{11}H_{11}O_4Cl_3$ requires C, 42·2; H, 3·5; Cl, 34·0%). It exhibits a negative ferric reaction in alcohol, does not give rise to a 2 : 4-dinitrophenylhydrazone under the usual conditions, and is stable to 2N-sodium hydroxide solution even on prolonged boiling.

Reduction of the ketone (1·5 g.) in methanol (10 ml.) during 15 minutes with concentrated hydrochloric acid (10 ml.), water (5 ml.) and zinc amalgam (5 g.) gave an almost quantitative yield of 1-ethyl-2 : 4 : 6-trimethoxybenzene, m. p. 28° (Dean and Nierenstein, *J. Amer. Chem. Soc.*, 1924, **46**, 2801, record m. p. 29—30°). When ω-trichloro-2 : 4-dihydroxy-6-methoxyacetophenone (0·5 g.) was treated during 6 hours in boiling acetone (50 ml.) with potassium carbonate (5 g.) and methyl sulphate (0·5 g.) the product was methyl 2 : 4 : 6-trimethoxybenzoate (0·3 g.), m. p. 70°, identical with an authentic specimen.

ω-Trichloro-4-hydroxy-2-methoxyacetophenone (IX).—A solution of resorcinol monomethyl ether (2 g.) and trichloromethyl cyanide (4 g.) gave this *ketone* (1·5 g.) in the usual way as rosettes of almost colourless prisms (from benzene), m. p. 144°, which exhibited a negative ferric reaction in alcohol and did not furnish a 2 : 4-dinitrophenylhydrazone under the usual conditions (Found : C, 40·0; H, 2·4; Cl, 39·7. $C_9H_7O_3Cl_3$ requires C, 40·2; H, 2·6; Cl, 39·5%). The mother-liquors from the crystallisation contained a small quantity of ω-trichloro-2-hydroxy-4-methoxyacetophenone, as indicated by the pale brown ferric reaction of the crude product, but the substance was present in quantity too small to be readily isolated.

The ketone readily dissolved in cold 2N-sodium hydrogen carbonate with immediate evolution of chloroform and quantitative production of 4-hydroxy-2-methoxybenzoic acid, m. p. 182° (decomp.). Bergmann and Dangschat (*Ber.*, 1919, **52**, 383) give m. p. 187—189° (decomp.).

ω-Trichloro-2-hydroxy-4 : 5-dimethoxyacetophenone (II; R = CCl_3).—When prepared similarly from 4-hydroxyveratrole (2 g.) and trichloromethyl cyanide (4 g.), this *compound* crystallised from aqueous methanol in shimmering, long, slender, yellow prisms (1 g.), m. p. 107°, easily soluble in alcohol, ether, and acetone, having a green-brown ferric reaction in alcohol, and furnishing no 2 : 4-dinitrophenylhydrazone under the usual conditions (Found : C, 40·2; H, 2·5. $C_{10}H_9O_4Cl_3$ requires C, 40·0; H, 3·0%). Its solution in cold 2N-sodium hydroxide immediately evolved chloroform, and on acidification furnished a quantitative yield of 2-hydroxy-4 : 5-dimethoxybenozic acid identical with an authentic specimen (Head and Robertson, *loc. cit.*).

When 1 drop of 50% potassium hydroxide was added to a suspension of the ketone (0·1 g.) in methanol (5 ml.) solution occurred immediately with the production of a quantitative yield of methyl 2-hydroxy-4 : 5-dimethoxybenzoate, m. p. 95—96°. Arnold and Bordwell (*J. Amer. Chem. Soc.*, 1942, **64**, 2983) record m. p. 95—96°.

2-Trichloroacetyl-6-hydroxy-3-methylcoumarone (XI; R = H, R′ = CCl_3).—6-Hydroxy-3-methylcoumarone (0·5 g.) and trichloromethyl cyanide (1 g.), etc., gave this *ketone* as pale greenish-yellow plates (0·3 g.) (from aqueous methanol), m. p. 180°, exhibiting a negative ferric reaction in alcohol and did not form a 2 : 4-dinitrophenylhydrazone under the usual conditions (Found : C, 45·2; H, 2·4; Cl, 35·4. $C_{11}H_7O_3Cl_3$ requires C, 45·1; H, 2·4; Cl, 36·3%). Treatment in boiling acetone with methyl

iodide–potassium carbonate during 3 hours gave a quantitative yield of *methyl 6-methoxy-3-methylcoumarone-2-carboxylate* (XI; R = Me, R′ = OMe) which separated in colourless needles, m. p. 90°, from aqueous methanol (Found: C, 65·6; H, 5·6. $C_{12}H_{12}O_4$ requires C, 65·5; H, 5·5%).

2-*Trichloroacetyl*-6-*methoxy*-3-*methylcoumarone* (XI; R = Me, R′ = CCl_3).—6-Methoxy-3-methylcoumarone (2 g.) similarly gave 2-*trichloroacetyl*-6-*methoxy*-3-*methylcoumarone* in long, slender, glistening, pale yellow prisms, m. p. 154°, did not give a 2 : 4-dinitrophenylhydrazone under the usual conditions and had a negative ferric reaction in alcohol (Found: C, 46·8; H, 2·8; Cl, 35·1. $C_{12}H_9O_3Cl_3$ requires C, 46·9; H, 2·9; Cl, 34·7%). Heating this ketone (1 g.) in 2N-sodium hydroxide (25 ml.) and methanol (5 ml.) on the steam-bath for 10 minutes gave chloroform and the 2-carboxylic acid, m. p. 190°, identical with an authentic specimen (Foster, Robertson, and Healey, *loc. cit.*).

A solution of the ketone (0·5 g.) in methanol (15 ml.) containing 60% potassium hydroxide solution (1 drop) was refluxed during 5 minutes, cooled, and diluted with water; ethyl 6-methoxy-3-methylcoumarone-2-carboxylate (0·4 g.) separated, having m. p. 70°, identical with an authentic specimen (Kostanecki and Lampe, *Ber.*, 1908, **41**, 1330). The methyl ester was similarly prepared in quantitative yield and was identical with an authentic specimen.

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143. *The Influence of Structure on the Ultra-violet Absorption Spectra of Heterocyclic Systems.*

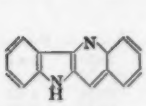
By G. R. CLEMO and D. G. I. FELTON.

The synthesis of a number of indoloquinolines is described. Their ultra-violet absorption spectra are recorded and compared with those of certain other related heterocyclic systems.

ULTRA-VIOLET absorption spectra have frequently been used as confirmatory evidence in the identification of heterocyclic compounds, but there are, as far as we are aware, comparatively few data available on heterocyclic systems possessing two or more hetero-atoms. A valuable survey of the simpler heterocyclic systems has been given by Braude (*Ann. Reports*, 1945, **42**, 128), in which these systems are compared with their carbocyclic analogues, but, apart from this, data are scattered in individual papers. Before the undoubtedly valuable potentialities of ultra-violet absorption spectra can be fully used as a diagnostic tool, a greater accumulation and empirical correlation of such data are necessary. It is for this reason that we present these results.

In the simplest heterocyclic systems, the spectral characteristics of those in which the nitrogen atom is bound to carbon by single bonds, *e.g.*, pyrrole, indole, carbazole, are not appreciably different from those of their carbocyclic analogues containing instead a methylene group. Similarly the series in which the nitrogen atom replaces a methine group, *e.g.*, pyridine, quinoline, acridine, show absorptions which are very similar to the aromatic analogues (Braude, *loc. cit.*). The similarity does not extend to cover the intensities which tend to be higher in the heterocyclic series owing to the increased mobility of the π electrons.

Fusion of two such systems might be expected to lead to modifications of the spectra, through the interaction of the two chromophoric systems. Such fused systems include the carbolines, pyrroloquinolines, indoloquinolines, and indolo*iso*quinolines, many of which have been found or postulated in alkaloids or alkaloid degradation products. A certain amount of information concerning the absorption of carbolines and pyrroloquinolines is to be found in the literature, but



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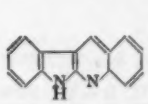

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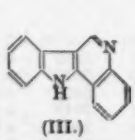

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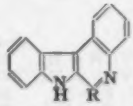
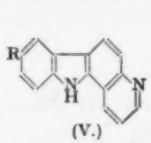


(IV.)

no information concerning that of indolo-quinolines or -*iso*quinolines is available. To date four of the possible fundamental indoloquinolines are known: indolo(3′ : 2′-2 : 3)quinoline (I) (" quindoline ") (Fichter and Rohner, *Ber.*, 1910, **43**, 3490; Noelting and Steuer, *ibid.*, p. 3512),

indolo(2′ : 3′-2 : 3)quinoline (II) (" quinindoline ") (Borsche, Wagner-Roemmich, and Barthenheier, *Annalen*, 1942, **550**, 160), indolo(3′ : 2′-3 : 4)quinoline (III) (3 : 4-quinindoline) (Clemo and Perkin, *J.*, 1924, **125**, 1608), and indolo(2′ : 3′-3 : 4)quinoline (IV; R = H) (Kermack and Slater, *J.*, 1928, 32). Recently Manske and Kulka (*Canad. J. Res.*, 1949, **27**, *B*, 291) have reported the synthesis of some indolo*iso*quinolines in which the indole moiety is fused to the benzenoid side of the *iso*quinoline molecule. Indoloquinolines in which the indole moiety is attached to the benzenoid ring of quinoline have been prepared in the form of their tetrahydro-compounds (Nandi, *J. Indian Chem. Soc.*, 1940, **17**, 449; Dewar, *J.*, 1944, 615).

In this study we have prepared indolo(2′ : 3′-5 : 6)quinoline (V; R = H), indolo(3′ : 2′-5 : 6)quinoline (VI; R = H), indolo(3′ : 2′-7 : 8)quinoline (VII; R = H), and their respective 5′-methyl homologues (V, VI, and VII; R = Me), from the 5-, 6-, and 8-quinolylhydrazones of *cyclo*hexanone (or 4-methyl*cyclo*hexanone) by ring closure with sulphuric acid in acetic acid, followed by dehydrogenation of the resultant tetrahydroindoloquinolines by means of palladised charcoal. The assumption is made in the case of (VI), where ring closure may occur in two ways, that it does so to yield the angular compound.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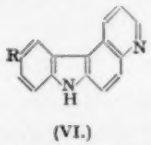
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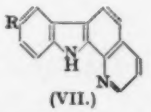

(VII.)

We have also prepared indolo(2′ : 3′-3 : 4)quinoline (IV; R = H) by a modification of Kermack and Slater's method (*loc. cit.*) which is simpler and offers higher yields. This procedure starts with the phenylhydrazone of ethyl *o*-nitrophenylpyruvate which undergoes the Fischer indole ring closure on boiling an ethanolic solution saturated with hydrogen chloride, to yield the crystalline ethyl 3-*o*-nitrophenylindole-2-carboxylate (previously reported as an oil). This on reduction over Adams's platinic oxide catalyst readily yields, by elimination of ethanol during the reduction, 2-hydroxyindolo(2′ : 3′-3 : 4)quinoline [1 : 2-dihydro-2-ketoindolo(2′ : 3′-3 : 4)quinoline]; replacement of oxygen by chlorine is effected by phosphorus pentachloride in phosphoryl chloride (Kermack and Tebrich, *J.*, 1940, 314) and this is then removed by catalytic hydrogenolysis. This procedure obviates the need for decarboxylation of the indole, followed by a Bischler–Napieralski type of ring closure of the reduced intermediate. The yields on each stage are of the order of 90% or more, and consequently indolo(2′ : 3′-3 : 4)quinoline is readily accessible. In contrast to the ease of reduction and simultaneous ring closure of ethyl 3-*o*-nitrophenylindole-2-carboxylate, the catalytic reduction of 3-*o*-nitrophenylindole-2-carboxylic acid proved very sluggish and yielded 3-*o*-aminophenylindole-2-carboxylic acid, which however, when heated, lost water by ring closure and in fact melted at the same temperature as the lactam.

The 2-methyl homologue (IV; R = Me) was prepared by the dehydrogenation of 4′ : 5′ : 6′ : 7′-tetrahydro-2-methylindolo(2′ : 3′-3 : 4)quinoline (Robinson and Robinson, *J.*, 1924, **125**, 837) by means of palladised charcoal. This preparation, involving the Fischer indole ring closure of the 3-quinaldylhydrazone of *cyclo*hexanone, was also adapted for the independent synthesis of (IV; R = H). 3-Quinolylhydrazine, from 3-aminoquinoline (Clemo and Swan, *J.*, 1945, 867), was condensed with *cyclo*hexanone, and the product cyclised with sulphuric acid in acetic acid to yield the tetrahydro-compound, which on dehydrogenation yielded (IV; R = H).

The ultra-violet absorption spectra of (IV, V, VI, and VII; R = H and Me in each case) were determined in ethanol, and the values of $\lambda_{max.}$ and $\log \varepsilon_{max.}$ are recorded in Table I (cf. Fig. 1).

TABLE I.

	$\lambda_{max.}$, A.	$\log \varepsilon_{max.}$	$\lambda_{max.}$, A.	$\log \varepsilon_{max.}$		$\lambda_{max.}$, A.	$\log \varepsilon_{max.}$	$\lambda_{max.}$, A.	$\log \varepsilon_{max.}$
(IV; R = H)	2590	4·61	3275	4·20	(VI; R = Me)	2480	4·40	2830	4·41
(IV; R = Me)	2580	4·58	3250	4·11				3450	3·97
(V; R = H)	2450	4·48	2920	4·58	(VII; R = H)	2430	4·58	2920	4·67
(V; R = Me)	2460	4·53	2970	4·57	(VII; R = Me)	2450	4·53	2940	4·60
(VI; R = H)	2455	4·48	2800	4·50					
			3410	3·98					

With the methyl homologues, there is in general a very slight bathochromic shift of *ca.* 20 A., with a very slight lowering of the intensity. Fig. 1 shows that the absorptions of the indolo-

quinolines in which the indole portion is attached to the benzenoid ring of the quinoline are fairly similar [(VI) has a third maximum where (V) and (VII) have inflexions], while there is a more profound difference when the indole system is fused to the heterocyclic ring of the quinoline. Thus there is a minimum in the case of (IV) where the others exhibit a maximum, though the inflexion shown by (V) and (VII) is reproduced by (IV), at a longer wave-length however. The close similarity between (V) and (VII) shows that the position in the quinoline ring of the heterocyclic nitrogen is of little consequence. A similar phenomenon is found in the benzoquinoline series (Johnson and Mathews, *J. Amer. Chem. Soc.*, 1944, **66**, 210).

The pyrroloquinolines, (VIII), (IX), and (X), corresponding to (V), (VI), and (VII) respectively, have been prepared and their absorption charted by Horner (*Annalen*, 1939, **540**, 73), while (XI), corresponding to (IV), has recently been reported by Eiter and Nagy (*Sitzungsber. Akad. Wien*, 1949, **158**, *IIb*, 607). These data are collected in Fig. 2. The striking difference

FIG. 1.

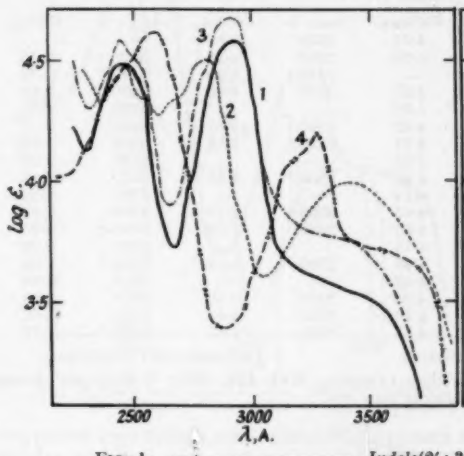


FIG. 2.

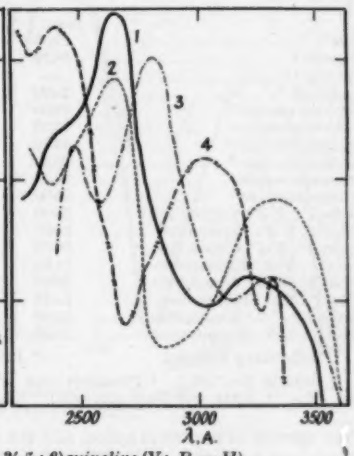
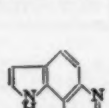
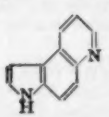


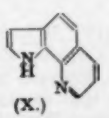
FIG. 1. ——————— *Indolo*(2′ : 3′-5 : 6)*quinoline* (V; R = H).
— — — — — — — — *Indolo*(3′ : 2′-5 : 6)*quinoline* (VI; R = H).
— · — · — · — · — *Indolo*(3′ : 2′-7 : 8)*quinoline* (VII; R = H).
× × — — × × — — *Indolo*(2′ : 3′-3 : 4)*quinoline* (IV; R = H).

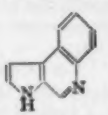
FIG. 2. ——————— *Pyrrolo*(2′ : 3′-5 : 6)*quinoline* (VIII).
— — — — — — — — *Pyrrolo*(3′ : 2′-5 : 6)*quinoline* (IX).
— · — · — · — · — *Pyrrolo*(3′ : 2′-7 : 8)*quinoline* (X).
× × — — × × — — *Pyrrolo*(2′ : 3′-3 : 4)*quinoline* (XI).

between the curve for the pyrroloquinoline (XI), in which the pyrrole ring is fused to the heterocyclic ring of the quinoline, and those of the other three, in which it is attached to the benzenoid ring, is again noteworthy though it is somewhat obscured by the differences between the latter three compounds. These differences are larger than those between their benzo-analogues (V, VI, and VII), but close scrutiny of Fig. 2 reveals the same general interrelation between the curves. Thus while pyrrolo(3′ : 2′-5 : 6)quinoline (IX) shows a pronounced maximum in the region of


(VIII.)


(IX.)


(X.)


(XI.)

3300 A., pyrrolo(2′ : 3′-5 : 6)- (VIII) and pyrrolo(3′ : 2′-7 : 8)-quinoline (X) show slight humps in this region, corresponding respectively to the pronounced maximum at 3400 A. for (VI) and the inflexions exhibited by (V) and (VII). That in fact it is the overall " shape " of the molecule

which determines the absorption is confirmed by the similarity in curves obtained with (IX) and (XI), though that of (IX) is shifted to longer wave-lengths; the same is partly true for (IV) and (VI), although there are complicating features in the spectra of (IV) and (XI), caused perhaps by the proximity of the heterocyclic rings.

Since the replacement of a methine group by a nitrogen atom produces only a slight change in absorption in the monoheteroatomic series, *e.g.*, pyridine, quinoline, compared with their aromatic analogues, we may look on the indolo- and pyrrolo-quinolines as isosterically related to indolo- and pyrrolo-naphthalenes and, simplifying still further, to naphthylamines. The conclusion reached concerning the " shape " of the above compounds then finds a logical basis since (V) and (VII), (VIII) and (X), the spectra of which appear to be closely related, are structural analogues of α-naphthylamine, while the other pairs, (IV) and (VI), (IX) and (XI), are modelled on β-naphthylamine. We may expect a closer resemblance to the corresponding aminoquinolines.

TABLE II.

	$\lambda_{max.}$, A.	log $\varepsilon_{max.}$	$\lambda_{max.}$, A.	log $\varepsilon_{max.}$	$\lambda_{max.}$, A.	log $\varepsilon_{max.}$
Indole [1]	2150	4·25	2650 f	3·80	—	—
Carbazole [2]	2420	4·38	2910	4·28	3300	3·50
Quinoline [1]	—	—	2750 f	3·65	3110 f	3·80
β-Carboline [3]	2400	4·60	2850	4·40	3400	3·85
α-Naphthylamine [3]	2400	4·08	—	—	3200	3·52
β-Naphthylamine [3]	2370	4·52	2800	3·61	3400	3·11
3-Aminoquinoline [3]	2420	4·21	2720 †	3·55	3500	3·45
5-Aminoquinoline [3]	2520	4·18	—	—	3430	3·20
6-Aminoquinoline [3]	2450	4·40	2800 *	3·45	3520	3·45
8-Aminoquinoline [3]	2590	4·18	—	—	3390	3·20
Pyrrolo(2′ : 3′-3 : 4)quinoline [4]	2400	4·65	3000	4·10	3300	3·60
Indolo(2′ : 3′-3 : 4)quinoline	2590	4·60	3275	4·20	3600 *	3·70
Pyrrolo(2′ : 3′-5 : 6)quinoline [5]	2650	4·70	—	—	3200	3·60
Indolo(2′ : 3′-5 : 6)quinoline	2450	4·48	2920	4·58	3350 *	3·60
Pyrrolo(3′ : 2′-5 : 6)quinoline [5]	2640	4·43	—	—	3310	3·98
Indolo(3′ : 2′-5 : 6)quinoline	2455	4·48	2800	4·50	3410	3·98
Pyrrolo(3′ : 2′-7 : 8)quinoline [5]	2480	4·10	2810	4·52	3300	3·60
Indolo(3′ : 2′-7 : 8)-quinoline	2430	4·58	2920	4·67	3300 *	3·76

f, Subsidiary maxima. * Inflexion. † Incipient point of inflexion.

[1] Braude (*loc. cit.*). [2] Pruckner and Witkop (*Annalen*, 1943, **554**, 130). [3] Steck and Ewing (*loc. cit.*). [4] Eiter and Nagy (*loc. cit.*). [5] Horner (*loc. cit.*).

The spectra of naphthylamines and the aminoquinolines have been studied very thoroughly by Steck and Ewing (*J. Amer. Chem. Soc.*, 1948, **70**, 3397). Data from their paper are included in Table II in which are summarised the principal bands of some of the heterocyclic systems containing two nitrogen atoms for comparison with the parent monoheteroatomic systems. The values of $\lambda_{max.}$ are grouped into sets of what appear to us to be comparable bands, although we do not attempt to correlate them to particular chromophoric systems.

For the pyrroloquinolines (VIII and IX) compared with the parent aminoquinolines, cyclisation to a pyrrole involves a bathochromic shift of about 100 A., though for (X) there is a corresponding hypsochromic shift of about the same amount with splitting of the first maximum. This is undoubtedly caused by interaction of the acidic pyrrole hydrogen with the basic quinoline nitrogen atom, as is to be expected from the basicity studies of the aminoquinolines carried out by Albert and Goldacre (*Nature*, 1944, **153**, 468). Addition of a further benzene ring, to give the indoloquinolines (V and VI), intensifies the bathochromic tendency and leads to the splitting of the first maximum into two maxima, one higher and the other lower in wave-length than the corresponding band in the pyrroloquinoline. The interaction of the acidic hydrogen of the indole with the basic nitrogen atom of the quinoline in (VII) is even more strongly marked than with the corresponding pyrroloquinoline, and there is a further hypsochromic shift of the first maximum.

Indolo(2′ : 3′-3 : 4)quinoline (IV; R = H) contains a β-carboline system. Fig. 3 shows its spectrum, along with that of β-carboline itself (Horner, *loc. cit.*; Pruckner and Witkop, *loc. cit.*), that of a typical carboline obtained from an indole alkaloid, *viz.*, yobyrine (Clemo and Swan, *J.*, 1946, 618), and also that of the pyrroloquinoline (XI) containing the analogous arrangement of heterocyclic rings. While the two true carbolines have very closely similar spectra, that of (IV) shows a bathochromic shift of about 250 A. and the shape of the minimum is considerably broadened; the shape of the second maximum, at 3275 A., closely resembles that of yobyrine at 2900 A., having a small peak on top and to the longer-wave side of a broad band.

A similar outline is reproduced in the third maximum of β-carboline at 3410 A., but this peak is probably not comparable with the other two. The pyrroloquinoline absorption is intermediate between that of (IV) and of β-carboline, the first maximum at 2400 A. being identical with β-carboline, while the second is not shifted so far towards longer wave-lengths as for (IV).

We have also studied the effect of a tetramethylene bridge on the absorption of the pyrroloquinoline (XI), by charting the spectra of 4′ : 5′ : 6′ : 7′-tetrahydroindolo(2′ : 3′-3 : 4)quinoline and its 2-methyl derivative (Fig. 4). The first maximum shows a slight hypsochromic tendency (maxima at 2315 A. and inflexions at *ca.* 2420 A.), while the second maximum undergoes a bathochromic shift of 200—250 A. (to 3200 and 3250 A. respectively). This is larger than the

FIG. 3.

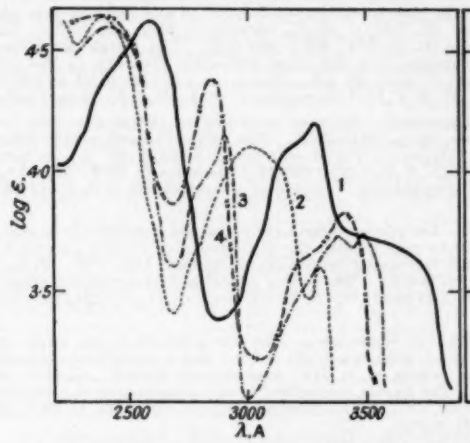


FIG. 4.

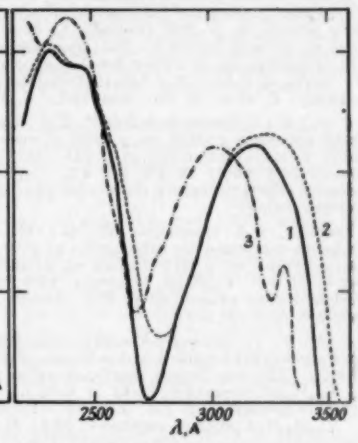


FIG. 3. ——————— *Indolo*(2′ : 3′-3 : 4)*quinoline* (IV; R = H).
— — — — — — — — *Pyrrolo*(2′ : 3′-3 : 4)*quinoline* (XI).
— · — · — · — · — *Yohimbine.*
× × — — × × — — β-*Carboline.*

FIG. 4. ——————— 4′ : 5′ : 6′ : 7′-*Tetrahydro*-2-*methylindolo*(2′ : 3′-3 : 4)*quinoline.*
— — — — — — — — 4′ : 5′ : 6′ : 7′-*Tetrahydroindolo*(2′ : 3′-3 : 4)*quinoline.*
— · — · — · — · — *Pyrrolo*(2′ : 3′-3 : 4)*quinoline.*

effect of alkyl groups in dienes (50 A. per alkyl substituent), but corresponds to the effect in the more mobile systems (100 A. per alkyl group) (Braude, *loc. cit.*, p. 120).

EXPERIMENTAL.

4′ : 5′ : 6′ : 7′-*Tetrahydroindolo*(2′ : 3′-5 : 6)*quinoline.*—5-Quinolylhydrazine dihydrochloride (5 g.) was condensed with *cyclo*hexanone (2·13 g.) in the presence of sodium acetate (5·91 g.), water (37 ml.), and ethanol (20 ml.) by refluxing the mixture on the steam-bath for 1 hour. The oily hydrazone obtained on cooling was extracted with chloroform, and the residue obtained on evaporation was cyclised by heating the solution in acetic acid (30 ml.) with sulphuric acid (2 ml.) at 100° for 10 minutes. The crystalline orange sulphate was collected and suspended in water, and the base liberated with aqueous ammonia, collected, and crystallised from aqueous pyridine, from which it was obtained in rectangular plates, m. p. 293—294° (Dewar, *loc. cit.*, gives m. p. 288—289°). The *picrate*, prepared in ethanol, crystallised from *cyclo*hexanone in minute yellow solvated prisms, m. p. 255° (decomp.) (Found, on a sample dried at 100°: C, 58·5; H, 4·8. $C_{15}H_{14}N_2,C_6H_3O_7N_3,0{\cdot}75C_6H_{10}O$ requires C, 58·3; H, 4·7. Found, on a sample dried at 180° in a vacuum: C, 56·8; H, 3·8; loss, 8·0. $C_{15}H_{14}N_2,C_6H_3O_7N_3,0{\cdot}25C_6H_{10}O$ requires C, 56·8; H, 4·1; loss, 9·3%).

Indolo(2′ : 3′-5 : 6)*quinoline* (V; R = H).—The above tetrahydro-compound (100 mg.) was intimately mixed with palladised charcoal (*ca.* 50 mg.) in a test-tube (3 × ¾″), and the tube, attached to the pump, was placed in a heated metal block. At 290—300°/10 mm., a white sublimate was obtained; this was remixed with the catalyst, and the mixture resublimed. The *product* (80 mg.) was removed and resublimed at 300°/10 mm., whereafter it formed long, very pale yellow prisms, m. p. 334—335° (decomp.) (Found: C, 82·4; H, 4·8; N, 12·6. $C_{15}H_{10}N_2$ requires C, 82·6; H, 4·6; N, 12·85%). The *picrate*, prepared in ethanol, crystallised from aqueous ethanol in microscopic yellow needles, m. p. 277° (decomp.) (Found: C, 55·7; H, 3·8. $C_{15}H_{10}N_2,C_6H_3O_7N_3,C_2H_5{\cdot}OH$ requires C,

56·0; H, 3·9. Found, in a sample dried at 120° in a vacuum: C, 56·6; H, 2·6. $C_{15}H_{10}N_2,C_6H_3O_7N_3$ requires C, 56·4; H, 2·9%).

4′ : 5′ : 6′ : 7′-Tetrahydro-5′-methylindolo(2′ : 3′-5 : 6)quinoline.—5-Quinolylhydrazine dihydrochloride (4·2 g.), sodium acetate (5·0 g.), and 4-methyl*cyclo*hexanone, condensed in aqueous ethanol, yielded an oily hydrazone, which after extraction was cyclised with sulphuric acid (2 ml.) in acetic acid (25 ml.). The *base*, liberated from the solid sulphate which was formed, crystallised from aqueous pyridine, forming flat needles, m. p. 298·5° (decomp.), after softening at 287° (Found: C, 81·6; H, 6·6. $C_{16}H_{16}N_2$ requires C, 81·4; H, 6·8%). The *picrate* formed minute rosettes of yellow microscopic needles (from *cyclo*hexanone), m. p. 259—260° (decomp.) (Found, on a sample dried at 100° in a vacuum: C, 58·5; H, 5·15. $C_{16}H_{16}N_2,C_6H_3O_7N_3,0{\cdot}5C_6H_{10}O$ requires C, 58·4; H, 4·7. Found, on a sample dried at 180° in a vacuum: C, 57·3; H, 4·05; loss, 9·9. $C_{16}H_{16}N_2,C_6H_3O_7N_3$ requires C, 56·8; H, 4·1; loss, 9·5%).

5′-Methylindolo(2′ : 3′-5 : 6)quinoline (V; R = Me).—Dehydrogenation over palladised charcoal at 300°/10 mm. yielded the *indoloquinoline*, which, after resublimation at 300°/10 mm., formed very pale yellow prisms, m. p. 335° (Found: C, 82·8; H, 5·0. $C_{16}H_{12}N_2$ requires C, 82·7; H, 5·2%). The mixed m. p. with indolo(2′ : 3′-5 : 6)quinoline (m. p. 334—335°) was 306°. The *picrate* crystallised from *cyclo*hexanone in yellow needles, decomposing over the range 280—287° (Found: C, 59·4; H, 4·2. $C_{16}H_{12}N_2,C_6H_3O_7N_3,0{\cdot}75C_6H_{10}O$ requires C, 59·5; H, 4·2. Found, on a sample dried at 180° in a vacuum: C, 57·5; H, 3·1; loss, 13·2. $C_{16}H_{12}N_2,C_6H_3O_7N_3$ requires C, 57·3; H, 3·25; loss, 13·8%).

4′ : 5′ : 6′ : 7′-Tetrahydroindolo(3′ : 2′-5 : 6)quinoline.—Prepared according to Dewar (*loc. cit.*), this formed colourless prisms, m. p. 205° (Dewar, m. p. 201—202°). The *picrate* formed orange-yellow needles (from *cyclo*hexanone), m. p. 241—242° (decomp.) (Found, on a sample dried at 180° in a vacuum: C, 56·6; 56·4, 56·5; H, 4·1, 4·1, 4·3. $C_{15}H_{14}N_2,C_6H_3O_7N_3,0{\cdot}25C_6H_{10}O$ requires C, 56·8; H, 4·1%). Strenuous efforts to remove the solvent proved unavailing. Drying at a temperature in excess of 180° led to darkening.

Indolo(3′ : 2′-5 : 6)quinoline (VI; R = H).—Dehydrogenation over palladised charcoal of the above tetrahydro-compound by sublimation at 270°/10 mm. yielded the *indoloquinoline* as very pale yellow massive prisms, m. p. 211° (mixed m. p. with the parent tetrahydro-compound, 178—179°) (Found: C, 82·7; H, 4·7. $C_{15}H_{10}N_2$ requires C, 82·6; H, 4·6%). The *picrate* crystallised from aqueous ethanol in bright yellow prisms, m. p. 275° (decomp.) (Found: C, 54·2; H, 3·6. $C_{15}H_{10}N_2,C_6H_3O_7N_3,H_2O$ requires C, 54·2; H, 3·2%).

4′ : 5′ : 6′ : 7′-Tetrahydro-5′-methylindolo(3′ : 2′-5 : 6)quinoline.—This was obtained in the usual way from 6-quinolylhydrazine dihydrochloride (6·0 g.), sodium acetate (7·1 g.), and 4-methyl*cyclo*hexanone (2·9 ml.). The *base* formed short pale yellow prisms, m. p. 258°, from acetone (Found: C, 81·6; H, 7·2. $C_{16}H_{16}N_2$ requires C, 81·4; H, 6·8%). The *picrate* crystallised from *cyclo*hexanone in clumps of small, fine needles, m. p. 254° (decomp.) (Found, on a sample dried at 180° in a vacuum: C, 56·5; H, 4·1. $C_{16}H_{16}N_2,C_6H_3O_7N_3$ requires C, 56·8; H, 4·1%).

5′-Methylindolo(3′ : 2′-5 : 6)quinoline (VI; R = Me).—Dehydrogenation at 280°/10 mm. over palladised charcoal and resublimation at 270°/10 mm. afforded this *compound* as pale yellow massive needles, m. p. 307° (slight decomp.) (Found: C, 82·5; H, 5·2. $C_{16}H_{12}N_2$ requires C, 82·7; H, 5·2%). The *picrate* formed very small bright yellow needles, m. p. 270° (decomp.), from *cyclo*hexanone (Found: C, 58·2; H, 3·6. $C_{16}H_{12}N_2,C_6H_3O_7N_3,0{\cdot}25C_6H_{10}O$ requires C, 58·1; H, 3·6. Found, on a sample dried at 180° in a vacuum: C, 57·1; H, 3·1. $C_{16}H_{12}N_2,C_6H_3O_7N_3$ requires C, 57·3; H, 3·25%).

4′ : 5′ : 6′ : 7′-Tetrahydroindolo(3′ : 2′-7 : 8)quinoline.—Prepared in the usual manner, this base formed large, lustrous prisms, m. p. 151—152°, from ethyl acetate (Dewar, *loc. cit.*, gives m. p. 151°). The *picrate* crystallised from *cyclo*hexanone as fine, deep-yellow needles, m. p. 250° (decomp.) (Found: C, 57·6; H, 4·4. $C_{15}H_{14}N_2,C_6H_3O_7N_3,0{\cdot}5C_6H_{10}O$ requires C, 57·6; H, 4·4. Found, on a sample dried at 180° in a vacuum: C, 56·1; H, 3·6. $C_{15}H_{14}N_2,C_6H_3O_7N_3$ requires C, 55·9; H, 3·8%).

Indolo(3′ : 2′-7 : 8)quinoline (VII; R = H).—After dehydrogenation of the tetrahydro-compound in the usual manner at 270°/10 mm., the resublimed product formed white needles, m. p. 165° depressed to 141—144° on admixture with the parent tetrahydroindoloquinoline (m. p. 151—152°). Recrystallisation from ethanol afforded *indolo(3′ : 2′-7 : 8)quinoline* as very long, silky, white needles, m. p. 169° (Found: C, 82·3; H, 4·9; N, 12·8. $C_{15}H_{10}N_2$ requires C, 82·6; H, 4·6; N, 12·85%). The *picrate* formed spherular clusters of small needles, m. p. 265° (decomp.), from *cyclo*hexanone (Found, on a specimen dried at 100° in a vacuum: C, 58·9, 58·9; H, 4·0, 3·8. $C_{15}H_{10}N_2,C_6H_3O_7N_3,0{\cdot}75C_6H_{10}O$ requires C, 58·8; H, 3·9. Found, on a sample dried at 180° in a vacuum: C, 56·6; H, 3·1. $C_{15}H_{10}N_2,C_6H_3O_7N_3$ requires C, 56·4; H, 2·9%).

4′ : 5′ : 6′ : 7′-Tetrahydro-5′-methylindolo(3′ : 2′-7 : 8)quinoline.—Prepared in the usual way from 8-quinolylhydrazine dihydrochloride and 4-methyl*cyclo*hexanone, this *base* crystallised from ethyl acetate, in which it was considerably soluble, in pale yellow needles, m. p. 152° (Found: C, 81·7; H, 6·65. $C_{16}H_{16}N_2$ requires C, 81·4; H, 6·8%). The *picrate* crystallised from *cyclo*hexanone as very fine, deep yellow needles, m. p. *ca.* 250° with preliminary darkening and decomposition at 230—240° (Found, on a sample dried at 180° in a vacuum: C, 57·1; H, 4·3. $C_{16}H_{16}N_2,C_6H_3O_7N_3$ requires C, 56·8; H, 4·1%).

5′-Methylindolo(3′ : 2′-7 : 8)quinoline (VII; R = Me).—Dehydrogenation was accomplished by sublimation from palladised charcoal at 250°/10 mm. After resublimation, the *indoloquinoline* formed colourless needles, m. p. 193—194° (Found: C, 82·4; H, 5·0; N, 12·3. $C_{16}H_{12}N_2$ requires C, 82·7; H, 5·2; N 12·1%). The *picrate* separated from *cyclo*hexanone as bright yellow needles, decomposing above 220° with no definite m. p. (Found: C, 59·1; H, 3·9. $C_{16}H_{12}N_2,C_6H_3O_7N_3,0{\cdot}5C_6H_{10}O$ requires C, 58·8; H, 3·9. Found, in a sample dried at 180° in a vacuum: C, 58·1; H, 3·7. $C_{16}H_{12}N_2,C_6H_3O_7N_3,0{\cdot}25C_6H_{10}O$ requires C, 58·1; H, 3·6%).

3-Quinolylhydrazine.—3-Aminoquinoline (Clemo and Swan, *J.*, 1945, 867) (1·0 g.) in concentrated hydrochloric acid (10 ml.) and water (4 ml.) was diazotised with sodium nitrite (0·5 g.) in water (17 ml.) and reduced by addition to stannous chloride (4·8 g.) in concentrated hydrochloric acid (5 ml.) and water (8·5 ml.). The tin was removed by precipitation with hydrogen sulphide, and the filtrate and washings were concentrated under reduced pressure and basified with sodium hydroxide solution (40%) with cooling. The solution was extracted with ethyl acetate and after being dried ($MgSO_4$), the extract was evaporated and *3-quinolylhydrazine* crystallised from ethyl acetate as frond-like fawn needles, m. p. 176—177° (Found : C, 67·9; H, 5·3. $C_9H_9N_3$ requires C, 67·9; H, 5·7%).

cyclo*Hexanone* *3-Quinolylhydrazone.*—This was obtained by condensing 3-quinolylhydrazine (0·8 g.) with *cyclo*hexanone (0·5 g.) in ethanol at 100° for 3 minutes in the presence of a trace of acetic acid. Dilution with water yielded the *hydrazone*, which formed pale yellow lozenge-shaped plates, m. p. 150—151°, from aqueous ethanol (Found : C, 75·1; H, 7·0. $C_{15}H_{17}N_3$ requires C, 75·3; H, 7·1%).

4′ : 5′ : 6′ : 7′-Tetrahydroindolo(2′ : 3′-3 : 4)quinoline.—The above hydrazone (0·4 g.) was cyclised by sulphuric acid (5 drops) in acetic acid (2 ml.). The *product* was precipitated by the addition of ammonia and after drying was dissolved in benzene and run on to a column of alumina, and impurities were removed by exhaustive elution with benzene. The alumina was then dried and extracted continuously with methanol. Evaporation of the solvent afforded a crystalline residue, which was sublimed at 260°/10 mm. to yield very pale cream-coloured needles, m. p. 265—266° (Found : C, 80·6; H, 6·15. $C_{15}H_{14}N_2$ requires C, 81·1; H, 6·3%).

Indolo(2′ : 3′-3 : 4)quinoline (IV; R = H).—Dehydrogenation of the tetrahydro-compound yielded nearly colourless needles, m. p. 249°, undepressed on admixture with an authentic specimen (see below).

2-Methylindolo(2′ : 3′-3 : 4)quinoline (IV; R = Me).—The corresponding tetrahydro-compound (Robinson and Robinson, *loc. cit.*) on dehydrogenation in the usual way and resublimation at 240°/10 mm. yielded colourless prisms, m. p. 200—201° (Found : C, 82·6; H, 5·2. Calc. for $C_{16}H_{12}N_2$: C, 82·7; H, 5·2%). Kermack and Slater (*loc. cit.*) describe this product as pale yellow needles (from benzene–light petroleum), m. p. 204—205°.

Ethyl 3-*o*-*Nitrophenylindole-2-carboxylate.*—Ethyl *o*-nitrophenylpyruvate phenylhydrazone (5·0 g.) (Wislicenus and Thoma, *Annalen*, 1924, **436**, 45) in ethanol (20 ml.) was rapidly saturated with dry hydrogen chloride, and the solution refluxed on the water-bath for 30 minutes, becoming dark brown and ammonium chloride being precipitated. The solution was cooled and diluted and, after scratching, the precipitated brown oil formed an orange-yellow solid (4·3 g., 91%). On crystallisation from ethanol, the *indole* ester formed orange-yellow needles, m. p. 131° (Found : C, 65·5; H, 4·7. $C_{17}H_{14}O_4N_2$ requires C, 65·8; H, 4·5%). Hydrolysis of the ester (2·0 g.) with alcoholic potash (20 ml. of 3%) for 2 hours, followed by acidification with dilute hydrochloric acid, yielded the corresponding acid, crystallising from ethanol as yellow needles, m. p. 274° (Kermack and Slater give m. p. 276°) (Found : C, 63·5; H, 3·55. Calc. for $C_{15}H_{10}O_4N_2$: C, 63·8; H, 3·55%).

2-Hydroxyindolo(2′ : 3′-3 : 4)quinoline (IV; R = OH).—The foregoing ester (6 g.) in ethyl acetate (70 ml.) was hydrogenated over Adams's platinic oxide at room temperature and 6 atms. Evaporation of the filtered solution, followed by crystallisation of the residue from methanol, afforded the lactam (yield, quantitative) as colourless needles, m. p. 313° (Kermack and Slater, *loc. cit.*, record m. p. >316°) (Found : C, 77·0; H, 4·4. Calc. for $C_{15}H_{10}ON_2$: C, 76·9; H, 4·3%).

3-*o* *Aminophenylindole-2-carboxylic Acid.*—Reduction of 3-*o*-nitrophenylindole-2-carboxylic acid (2 g.) in ethyl acetate (40 ml.) by hydrogen and platinic oxide (room temperature, 6 atms.) was extremely slow. A white precipitate formed during the reduction was taken up in more ethyl acetate, and the hot solution freed from catalyst by filtration. Evaporation left a white solid, which on crystallisation from acetic acid yielded the *indole amino-acid* as colourless thin rods, m. p. 312—313° (effervs.) (Found : C, 71·8; H, 4·7. $C_{15}H_{12}O_2N_2$ requires C, 71·4; H, 4·8%).

Indolo(2′ : 3′-3 : 4)quinoline (IV; R = H).—The lactam obtained above (1 g.) was converted into the corresponding chloro-compound, needles (from benzene), m. p. 185° (Kermack and Tebrich, *loc. cit.*, give m. p. 182°), by means of a mixture of phosphorus pentachloride (2·5 g.) in phosphoryl chloride (10 ml.) at 130° under reflux. The chloro-compound, dissolved in acetic acid, was hydrogenated over palladised charcoal at room temperature and 6 atms. The solution, after removal of the catalyst, was very pale yellow with a very intense, brilliant blue-green fluorescence. After removal of the solvent, the base was liberated from its hydrochloride and purified by sublimation at 250°/10 mm., forming colourless silky needles, m. p. 249° (Found : C, 82·7; H, 4·5. Calc. for $C_{15}H_{10}N_2$: C, 82·6; H, 4·6%). Kermack and Slater (*loc. cit.*) describe the compound as pale yellow needles (from benzene), m. p. 245°.

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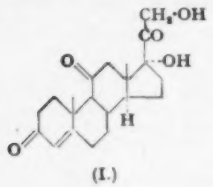
144. *Steroids and Related Compounds. Part XI. Some Derivatives of Zymosterol.*

By (Mrs.) W. J. Adams, V. Petrow, and R. Royer.

The possibility of introducing an oxygen atom at position 11 of a $\Delta^{8(9)}$-steroid has been examined.

Reaction of zymost-8-enol (III) with selenium dioxide failed to give the 11-hydroxy-compound, the dehydro-compound (IV) being obtained. Chromic acid oxidation of zymosteryl acetate dibromide was likewise unsuccessful, a keto-group being introduced at $C_{(7)}$.

The direct introduction of an oxygen atom at position 11 of a steroid substituted at positions 3 and 17 would form an attractive route to compounds such as Cortisone (I). Such a reaction has indeed been realised biochemically: when 11-deoxycorticosterone is perfused through isolated adrenal glands, corticosterone is recovered from the perfusates (Hechter, Jacobsen, Jeanloz, Levy, Marshall, Pincus, and Schenker, *J. Amer. Chem. Soc.*, 1949, **71**, 3261). Though highly significant from the biogenetic standpoint, this method is not applicable practically,



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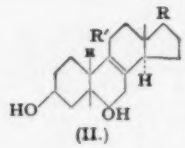

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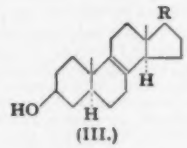

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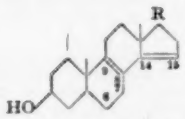

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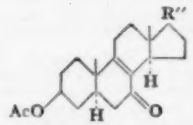

(V.)

(R = C_8H_{17}; R″ = CHMe·[CH_2]$_3$·CH:CMe_2)

and the markedly selective character of bio-oxygenation processes lends small encouragement to the existence of chemical equivalents. Direct chemical oxidation at $C_{(11)}$ would almost certainly require the presence of a contiguous activating ethylenic grouping at position 8 : 9, a point well illustrated by results obtained in the " Westphalen series " in which 3 : 6-dihydroxy-5-methyl-10-norcholest-8(9)-ene (II; R′ = H) is converted into the 3 : 6 : 11-trihydroxy-derivative (II; R′ = OH) by selenium dioxide (Petrow, *J.*, 1939, 998; Davies and Petrow, *J.*, 1949, 2973). We therefore turned our attention to model experiments employing zymost-8-enol (III), a fairly accessible steroid of the required type.

Reaction of (III) with selenium dioxide occurred readily in boiling ethanol. In contrast to the results with (II; R = H), however, oxidation failed to give an 11-hydroxy-compound, and a dehydrozymostenol, m. p. 119—120°, $[\alpha]_D$ −12·9° (in chloroform), was obtained instead in good yield. The ultra-violet absorption spectrum of this compound showed it to be a hetero-annular conjugated diene. The unsaturated linkages may, therefore, be at 8 : 14, 7 : 9(11), 6 : 8(14) or 7 : 14. Of these, the last is eliminated by the failure of the compound to react with maleic anhydride. The 7 : 9(11) and 6 : 8(14) formulations are likewise rendered improbable by the low negative rotation of the dehydro-stenol (cf. Eck and Hollingsworth, *J. Amer. Chem. Soc.*, 1942, **64**, 140; Barton, *J.*, 1946, 512). The compound may, therefore, be assigned the constitution of cholesta-8 : 14-dien-3β-ol (IV).

The formulation (IV) had previously been assigned by Heath-Brown, Heilbron, and Jones (*J.*, 1940, 1482) to a " dehydro-α-zymostenol," m. p. 98—99°, $[\alpha]_D$ −9·1° (in chloroform), obtained by selenium dioxide oxidation of α-zymostenol [cholest-8(14)-en-3β-ol]. Evidence supporting this structure, however, was limited to spectroscopic study and to analogy with the known behaviour of α-ergostenol under similar experimental conditions (Callow, *J.*, 1936, 462). Employing larger quantities of material, we now find " dehydro-α-zymostenol " to be

dentical in melting point, etc., with our dehydrozymostenol, the constitution of which may, therefore, be considered as finally established.

Chromic acid oxidation of the Δ^8-stenol appeared to offer another potential route to 11-oxygenated compounds of the desired type. The possibility of such a reaction had previously been discussed by Stavely and Bollenback (*J. Amer. Chem. Soc.*, **1943**, **65**, 1290) who studied the oxidation of "α"-dihydroergosterol, regarded by them as a $\Delta^{8(9)}$-stenol. The formulation assigned to this compound, however, has since proved to be incorrect (cf. Wieland and Benend, *Annalen*, **1943**, **554**, 1) so that conclusions based on this evidence must be accepted with caution. Chromic acid oxidation of the Westphalen diacetate (cf. II; R = H) leads readily to the corresponding 11-ketone 8 : 9-oxide (Petrow, *loc. cit.*). Experiments on the oxidation of zymosteryl acetate dibromide proved only partly successful, owing to profound degradation of the molecule. Debromination of the product, followed by chromatography, however, led to the isolation of a new αβ-unsaturated ketone, although in very low yield. Its formulation as 7-ketozymosteryl acetate (V) followed from its conversion into a 2 : 4-dinitrophenylhydrazone, and the observation (Fieser and Fieser, "Products Related to Phenanthrene," Rheinhold Publ. Corpn., 3rd edn., p. 229) that oxidation of compounds with a ditertiary double bond never involves the migration of the double bond from its original position.

Reaction between zymost-8-enol and *N*-bromosuccinimide, mercuric chloride, or lead tetra-acetate failed to give products which could be characterised.

The foregoing results point strongly to the conclusion that effective activation of the $C_{(11)}$-methylenic grouping cannot be achieved by introduction of an unsaturated linkage in the 8(9)-position. The steric hindrance of the angular methyl grouping at $C_{(10)}$ cannot, of course, be excluded from consideration as an inhibiting factor in the desired conversions. Nevertheless, Fieser's recent postulates (*Experientia*, **1950**, **6**, 312) on this matter do not support the view that steric effects, *per se*, will prevent the admission of groups at $C_{(11)}$ provided that such entrance occurs from the less-hindered rear side of the molecule.

Experimental.

M. p.s are uncorrected. Optical rotation were measured in chloroform solution in a 2-dm. tube. Ultra-violet absorption spectra were kindly determined by Dr. R. Stuckey and Mr. P. Stross, B.Sc., Analytical Department, The British Drug Houses, Ltd.

Preparation of Zymost-8-enol (III).—Consistently improved yields of zymost-8-enol were obtained by employing the general technique of Wieland, Rath, and Benend (*Annalen*, 1941, **548**, 19) but using platinum oxide catalyst prepared as described by Cook and Linstead (*J.*, 1934, 946).

Reduction of Zymosterol Dibromide.—The following unsuccessful attempts were made to prepare zymost-8-enol by reduction of zymosterol dibromide.

(i) Zymosterol dibromide (2 g.), suspended in benzene (25 ml.), potassium hydroxide solution (0·55 g. in 1 ml. of water), ethanol (100 ml.), and Raney nickel were shaken with hydrogen. Absorption (90 ml.) was complete in *ca.* 1½ hours. Zymosterol, m. p. 108—110° (93%), was recovered from the filtered solution.

(ii) A suspension of zymosterol dibromide (0·17 g.) in dry benzene (40 ml.) was added to a solution of lithium aluminium hydride in ether (25 ml. of 0·7%), and the mixture heated under reflux for 1 hour. The product was treated with water and acidified to Congo-red with 3N-sulphuric acid, and the material recovered in the usual way. Crystallisation from methanol gave zymosterol, m. p. 108—109° (91%), converted into the acetate, m. p. 103—104°, both compounds showing no m. p. depression on admixture with authentic specimens.

Dehydrozymost-8-enol (*Cholesta*-8 : 14-*dien*-3β-*ol*) (IV).—Zymost-8-enol (8·0 g.) in boiling ethanol (200 ml.) was treated with selenium dioxide (8·0 g.) in water (25 ml.), and the mixture heated under reflux for 1 hour. Precipitated selenium was removed by filtration, the mixture taken to dryness, and residual selenium removed by passage of a benzene solution through a short alumina column (½ × 1″). Crystallisation from methanol (Kieselguhr) gave dehydrozymost-8-enol (60%), small needles, double m. p. 119—120° and 125—126°, $[\alpha]_D^{24}$ −12·9° (*c*, 0·580), $\lambda_{max.}$ 250 mμ., log ε = 4·3 in alcohol (Found : C, 84·9; H, 11·4. $C_{27}H_{44}O$ requires C, 84·3; H, 11·5%). The *acetate* separated from methanol in plates, m. p. 101—102°, $[\alpha]_D^{23\cdot5}$ −22·9° (*c*, 0·553) (Found : C, 81·9; H, 10·7. $C_{29}H_{46}O_2$ requires C, 81·6; H, 10·9%). The *benzoate*, crystallised from acetone, had m. p. 147—148°, $[\alpha]_D^{23}$ −6·9° (*c*, 0·594) (Found : C, 83·5; H, 9·8. $C_{34}H_{48}O_2$ requires C, 83·6; H, 9·9%).

Dehydro-α-zymostenol.—Prepared from α-zymostenol as described above, the compound formed small needles (40%), m. p. 119—120° and 125—126°, $[\alpha]_D^{26}$ −13·7° (*c*, 0·615), $\lambda_{max.}$ 250 mμ., log ε = 4·3 in alcohol. The acetate formed plates (from methanol), m. p. 101—102°, $[\alpha]_D^{16}$ −23·2° (*c*, 0·494) (Found : C, 82·1 : H, 10·6%). The benzoate had m. p. 147—148°, $[\alpha]_D^{20}$ −6·5° (*c*, 0·388) (Found : C, 83·2; H, 9·7%). The compounds gave no depression on admixture with the corresponding derivatives prepared from zymost-8-enol.

Zymosteryl Acetate Dibromide.—Zymosterol dibromide (2·7 g.) in pyridine solution (50 ml.) was treated with acetic anhydride (14 ml.) for 12 hours at room temperature. Crystallisation of the product from chloroform–ethanol gave zymosteryl acetate dibromide, m. p. 169°, $[\alpha]_D^{17\cdot5}$ +5·9° (*c*, 0·603) (Found :

C, 59·6; H, 7·9; Br, 26·8. Calc. for $C_{29}H_{46}O_3Br_2$: C, 59·4; H, 7·9; Br, 27·2%). Reindel and Weichmann (*Annalen*, 1930, **482**, 120) give m. p. 168—169° (corr.), $[\alpha]_{4461}$ −9·7°.

7-*Ketozymosteryl Acetate* (V).—(i) A suspension of zymosteryl acetate dibromide (4·4 g.) in acetic acid (100 ml.) and acetic anhydride (5 ml.) at 54° was treated, with stirring, with powdered chromium trioxide (3·1 g.) added during 1 hour. After a further 2 hours at this temperature the mixture was diluted with water and extracted with ether, and the ethereal layer washed successively with water, 5% aqueous ammonia, and water, then dried, and the ether removed. The resulting residue in ethanol (200 ml.) was heated under reflux with activated zinc (13 g.) for 1 hour and the resulting product, in benzene solution, passed through a column (8 × 1") of activated alumina (B.D.H.). Removal of the benzene, followed by crystallisation from methanol, gave 7-*ketozymosteryl acetate*, needles (50 mg.), m. p. 135—136°, $[\alpha]_D^{21}$ −32·2° (*c*, 0·815); $\lambda_{max.}$ 252 mμ., log ε = 4·0 in alcohol (Found: C, 78·8; H, 9·6. $C_{29}H_{44}O_3$ requires C, 79·1; H, 10·0%).

The 2 : 4-*dinitrophenylhydrazone* formed orange needles (from ethanol), m. p. 227° (decomp.) (Found: C, 67·5; H, 7·5; N, 9·4. $C_{35}H_{48}O_6N_4$ requires C, 67·7; H, 7·7; N, 9·0%).

(ii) Zymosteryl acetate dibromide was oxidised as described above and the product isolated with ether. Trituration with boiling acetone gave crude 7-ketozymosteryl acetate dibromide (2·7 g.), m. p. 176—178°, which could not be freed from a persistent impurity. Treatment with 2 : 4-dinitrophenylhydrazine gave 7-*ketozymosteryl acetate dibromide* 2 : 4-*dinitrophenylhydrazone*, orange needles (from ethanol), m. p. 196—198° (Found: C, 53·8; H, 6·1; N, 7·3. $C_{35}H_{48}O_6N_4Br_2$ requires C, 53·8; H, 6·1; N, 7·2%). Debromination of the crude 7-ketozymosteryl acetate dibromide led to 7-ketozymosteryl acetate, m. p. 134—135°, not depressed on admixture with a sample prepared as in (i).

The authors thank the Directors of The British Drug Houses, Ltd., for permission to publish these results.

The Research Laboratories, The British Drug Houses, Ltd.,
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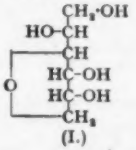
145. *Some Derivatives of* 3 : 6-*Anhydromannitol.*

By A. B. Foster and W. G. Overend.

Several derivatives suitable for the characterization of 3 : 6-anhydromannitol are described. The graded acid hydrolysis of 1 : 2-4 : 5-di*iso*propylidene 3 : 6-anhydromannitol yields 4 : 5-*iso*propylidene 3 : 6-anhydromannitol, the structure of which is proved. Oxidation of this by lead tetraacetate affords derivatives of 2 : 5-anhydro-D-arabinose, the stability of which towards hydrochloric acid has been studied. The exchange reactions with iodine of ditoluene-*p*-sulphonyl and dimethanesulphonyl derivatives of 4 : 5-*iso*propylidene 3 : 6-anhydromannitol have been examined.

It is well known that the action of acids on mannitol results in the formation of a mixture of anhydromannitol derivatives. Although examined by numerous workers (Fauconnier, *Bull. Soc. chim.*, 1884, **41**, 119; *Compt. rend.*, 1885, **100**, 914; Romburgh and Burg, *Proc. Acad. Sci. Amsterdam*, 1922, **25**, 335; Wiggins, *J.*, 1945, 4; Montgomery and Wiggins, *J.*, 1948, 2204), the composition of this mixture has not been completely elucidated. However it is known that 3 : 6-anhydromannitol (mannitan) (I) is present in small but varying amounts. It was first obtained by Fauconnier (*loc. cit.*) by the action of formic or hydrochloric acid on mannitol and its structure was conclusively proved when its identity with the product obtained by reduction of 3 : 6-anhydro-D-mannose was established (Valentin, *Coll. Czech. Chem. Comm.*, 1936, **8**, 35). Treatment of 3 : 6-anhydromannitol (I) with acetic anhydride in pyridine afforded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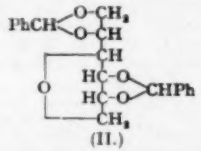
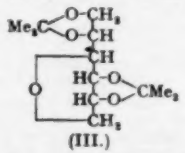
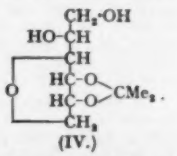

(II.)


(III.)

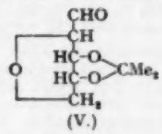

(IV.)

syrupy 1 : 2 : 4 : 5-tetra-acetyl 3 : 6-anhydromannitol, while a more convenient derivative for purposes of characterization was the crystalline 1 : 2 : 4 : 5-tetrabenzoate obtained by using benzoyl chloride in pyridine. (I) could readily be further characterized as its crystalline dibenzylidene derivative which was obtained by treatment with benzaldehyde either at room

temperature in the presence of zinc chloride or preferably at elevated temperatures in an inert atmosphere (cf. Honeyman and Oldham, *J.*, 1946, 986). This derivative is probably 1 : 2-4 : 5-dibenzylidene 3 : 6-anhydromannitol (II) and its structure will be discussed in a subsequent communication.

When 3 : 6-anhydromannitol (I) was shaken with acetone containing a suitable dehydrating agent 1 : 2-4 : 5-di*iso*propylidene 3 : 6-anhydromannitol (III) was obtained in good yield. The greater lability, towards acidic reagents, of *iso*propylidene residues engaging primary and secondary hydroxyl groups [*e.g.*, (III), positions $C_{(1)} : C_{(3)}$] compared with those engaging only secondary hydroxyl groups [*e.g.* (III), positions $C_{(4)} : C_{(5)}$] has been noted by several workers (cf. Wiggins, *J.*, 1946, 13). When (III) was dissolved in 70% aqueous acetic acid, partial hydrolysis occurred and a crystalline mono*iso*propylidene derivative of 3 : 6-anhydromannitol was obtained. That this was 4 : 5-*iso*propylidene 3 : 6-anhydromannitol (IV) was indicated by the liberation of formaldehyde (characterized by forming a derivative with dimedone) on oxidation with periodic acid (cf. Reeves, *J. Amer. Chem. Soc.*, 1941, **63**, 1476), thereby indicating the presence of the $CH_2(OH)\cdot CH(OH)\cdot$ grouping. Further hydrolysis of (IV) with mineral acid yielded 3 : 6-anhydromannitol (I). Moreover, it was shown that the rate of oxidation of (IV) by lead tetra-acetate in glacial acetic acid was closely analogous to that of an equimolecular amount of 1 : 2-*iso*propylidene D-glucofuranose. The product isolated from the lead tetra-acetate oxidation of (IV) was a liquid which readily polymerized, particularly on attempted distillation. It exhibited strong absorption in the ultra-violet region (at 2550 A.); this absorption is displaced from that normally associated with the carbonyl group (*i.e.*, 2900 A.), owing to the combined influence of the butylene oxide ring and the ketal residue. There can be little doubt that the product was 3 : 4-*iso*propylidene 2 : 5-anhydro*aldehydo*-D-arabinose (V). Treatment of (V) with N-hydrochloric acid at 100° removed the *iso*propylidene residue, yielding 2 : 5-anhydro-D-arabinose, represented in (VI) as the *aldehydo*-form. It was expected that the aldehyde group would render the adjacent anhydro-ring of (V) unstable and that on treatment with hydrochloric acid a 2-halogeno-2-deoxy-D-arabinose or 2-halogeno-2-deoxy-D-ribose would result. Either of these would form a useful precursor of 2-deoxy-D-ribose, an important sugar in biological processes (cf. Stacey *et al.*, *J.*, 1949, 1879, 2836). The ultra-violet absorption of the hydrolysis product (VI) showed a peak at 2680 A. and it may be deduced that (VI) contained a considerable proportion of the *aldehydo*-form, although it was much more weakly absorbing than (V). This was well substantiated by its treatment with methanolic hydrogen chloride, since the product isolated was not the αβ-methylglycoside which normally results from the action of this reagent on ring sugars, but the dimethyl acetal (VII). It is apparent therefore that the butylene oxide ring in 2 : 5-anhydro-D-arabinose (VI) tends to maintain the sugar in an open-chain structure, an effect similar to that encountered by Haworth, Jackson, and Smith (*J.*, 1940, 620) in the 3 : 6-anhydrohexose series.

4 : 5-*iso*Propylidene 3 : 6-anhydromannitol (IV) could also be characterized as the crystalline 1 : 2-diacetate and 1 : 2-di-*p*-nitrobenzoate. Similarly by treatment of (IV) with methane-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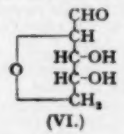
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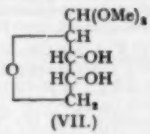
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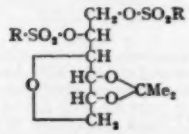
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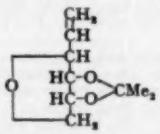
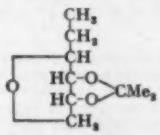

(IX.)


(X.)

sulphonyl chloride or toluene-*p*-sulphonyl chloride in dry pyridine the 1 : 2-dimethanesulphonyl and 1 : 2-ditoluene-*p*-sulphonyl derivatives (VIII; R = Me and C_6H_4Me, respectively) were obtained. The unusual reaction of terminal vicinal ditoluene-*p*-sulphonyl derivatives of simple carbohydrates with sodium iodide in acetone under standard conditions has been noted by several workers (Hann, Ness, and Hudson, *J. Amer. Chem. Soc.*, 1944, **66**, 73; Tipson and

Cretcher, *J. Org. Chem.*, 1943, **8**, 95; Karrer *et al.*, *Helv. Chim. Acta*, 1948, **31**, 784, 1611; Owen and Bladon, *J.*, 1950, 598): it involves elimination of the toluene-*p*-sulphonyl residues, liberation of iodine, and concomitant establishment of an ethylenic linkage. The 1 : 2-di-toluene-*p*-sulphonyl derivative (VIII) was heated with anhydrous acetone and sodium iodide at 125—130° for four hours, 1·84 moles of sodium toluene-*p*-sulphonate were precipitated, iodine was liberated, and the crystalline product isolated was 4 : 5-*iso*propylidene 3 : 6-anhydro-mannitoleen (IX). Attempts to prepare 1-iodo 4 : 5-*iso*propylidene 2-toluene-*p*-sulphonyl 3 : 6-anhydro-1-deoxymannitol by treating (VIII; R = C_6H_4Me) with one molecular proportion of sodium iodide in acetone under very mild conditions always resulted in precipitation of sodium toluene-*p*-sulphonate and concomitant liberation of iodine, the reactivities of the toluene-*p*-sulphonyloxy-groups being clearly similar. For comparative purposes both the 1 : 2-di-methanesulphonyl and 1 : 2-ditoluene-*p*-sulphonyl derivatives (VIII) were subjected to iodine-exchange reactions under identical, though milder, conditions than those normally employed; the latter derivative underwent 48·3% exchange and the former 43·3%; the difference in degree of exchange of methanesulphonyloxy- and toluene-*p*-sulphonyloxy-groups in standard reactions has been noted previously (Foster, Overend, Stacey, and Wiggins, *J.*, 1949, 2542) and this work is being extended.

Hydrogenation of 4 : 5-*iso*propylidene 3 : 6-anhydromannitoleen (IX) in the presence of platinum oxide readily gave 4 : 5-*iso*propylidene 3 : 6-anhydro-1 : 2-dideoxymannitol (X).

Experimental.

Action of Hydrochloric Acid on Mannitol.—Mannitol (500 g.) was boiled under reflux with concentrated hydrochloric acid (2 l.) for 24 hours. After being boiled for a further 10 minutes with activated charcoal (20 g.), the solution was filtered and evaporated to a syrup at 60—70° (bath-temp.)/12—15 mm. Traces of hydrochloric acid were removed as completely as possible by repeated addition of water and re-evaporation, and the ultimate straw-coloured syrup was dissolved in ethanol (400 c.c.), and set aside at 0° for several days. The impure product which separated was collected and washed several times with ethanol. Repeated recrystallization from aqueous ethanol gave a product, m. p. 136—137°, which still contained mannitol. Distillation gave a fraction, b. p. 220—230° (bath-temp.)/0·03 mm., which crystallized on storage and after recrystallization from aqueous ethanol was obtained as large colourless plates (30 g.). It was 3 : 6-anhydromannitol (mannitan), m. p. 146—147°, $[\alpha]_D^{20}$ −26·2° in water. (Wiggins, *loc. cit.*, gives m. p. 145—147° and Valentin, *loc. cit.*, records m. p. 146—147° for the product obtained by the reduction of 3 : 6-anhydro-D-mannose.)

1 : 2 : 4 : 5-*Tetra-acetyl* 3 : 6-*Anhydromannitol.*—A solution of mannitan (1·0 g.) in dry pyridine (5 c.c.) was treated with freshly distilled acetic anhydride (2 c.c.) at room temperature for 20 hours. The reaction mixture was diluted with water (50 c.c.) and extracted with chloroform (5 × 30 c.c.), and the extract washed with water and dried ($MgSO_4$). Evaporation of the solvent gave a straw-coloured syrup from which 1 : 2 : 4 : 5-*tetra-acetyl* 3 : 6-*anhydromannitol* (0·7 g.) was obtained, b. p. 170—175° (bath-temp.)/0·05 mm., n^{20} 1·4545, $[\alpha]_D^{20}$ +19·5° (*c*, 1·4 in chloroform) (Found: C, 50·8; H, 6·2. $C_{14}H_{20}O_9$ requires C, 50·6; H, 6·0%).

1 : 2 : 4 : 5-*Tetrabenzoyl* 3 : 6-*Anhydromannitol.*—Benzoyl chloride (0·82 c.c.) was cautiously added to a solution of mannitan (0·25 g.) in dry pyridine (2 c.c.), and the mixture set aside at room temperature for 5 hours. On dilution with water a syrupy product separated which did not solidify on trituration. However, when it was kept for a long time in acetone–water–ethanol colourless prisms of 1 : 2 : 4 : 5-*tetrabenzoyl* 3 : 6-*anhydromannitol* separated. After recrystallization this had m. p. 88—89° and $[\alpha]_D$ −157° (*c*, 1·5 in chloroform) (Found: C, 70·2; H, 4·9. $C_{34}H_{28}O_9$ requires C, 70·3; H, 4·8%).

Reaction of 3 : 6-*Anhydromannitol with Benzaldehyde.*—(a) *In the presence of anhydrous zinc chloride.* Mannitan (1·0 g.) was shaken with freshly distilled benzaldehyde (5 c.c.) and finely powdered, anhydrous zinc chloride (1·5 g.) at room temperature for 20 hours. The mixture was then treated with water and light petroleum (b. p. 60—80°), and the crystals which gradually separated were collected after 2 hours, washed alternately with the same solvents, and recrystallized from aqueous ethanol. 1 : 2-4 : 5(?)-*Dibenzylidene* 3 : 6-*anhydromannitol* (0·2 g., 9·65%) was obtained as colourless needles, m. p. 109—110°, $[\alpha]_D^{20}$ −86·4° (*c*, 0·5 in benzene) (Found: C, 69·7; H, 5·7. $C_{20}H_{20}O_6$ requires C, 70·6; H, 5·9%).

(b) *At elevated temperatures* (cf. Oldham and Honeyman, *loc. cit.*). A stream of carbon dioxide was passed through a mixture of benzaldehyde (5 c.c.) and mannitan (1·0 g.), heated at 140—145°, for 4 hours. Removal of the benzaldehyde by evaporation under diminished pressure gave a crystalline residue which was dissolved in benzene and freed from traces of benzoic acid by washing with dilute aqueous sodium hydroxide and then with water. The solution was dried ($MgSO_4$) and evaporated to dryness, yielding a residue (1·5 g., 72·4%) which after recrystallization from aqueous ethanol had m. p. 109—110° alone or on admixture with the product from (*a*) and $[\alpha]_D^{20}$ −88·1° (*c*, 1·5 in benzene). Valentin (*loc. cit.*) reports a benzylidene derivative of 3 : 6-anhydromannitol having m. p. 125—126° and $[\alpha]_D$ −48·8° in chloroform.

1 : 2-4 : 5-*Diisopropylidene* 3 : 6-*Anhydromannitol.*—3 : 6-Anhydromannitol (5 g.) was shaken mechanically for 48 hours with dry acetone (100 c.c.) containing anhydrous zinc chloride (6 g.) and a homogeneous mixture of syrupy phosphoric acid (3 c.c.) and phosphoric oxide (1·5 g.). The solution was poured into water containing an excess of sodium carbonate and the precipitated zinc carbonate

collected and washed with acetone. The combined filtrate and washings were evaporated under diminished pressure until the acetone had been completely removed, and the remaining aqueous solution was extracted with ether (5 × 100 c.c.). Evaporation of the extract after drying ($MgSO_4$) gave a syrupy residue, from which the *diisopropylidene* derivative (5·18 g.) was obtained as a colourless mobile liquid, b. p. 95—100° (bath-temp.)/0·01 mm., n^{18} 1·4555, $[\alpha]_D^{20}$ −53·4° (*c*, 2·1 in chloroform) (Found : C, 58·8; H, 8·2. $C_{12}H_{20}O_5$ requires C, 59·0; H, 8·2%).

4 : 5-iso*Propylidene* 3 : 6-*Anhydromannitol*—1 : 2-4 : 5-Diisopropylidene 3 : 6-anhydromannitol (2·1 g.) was dissolved in a solvent (40 c.c.) prepared by adding water (30 c.c.) to glacial acetic acid (70 c.c.), and the hydrolysis followed polarimetrically {$[\alpha]_D^{20}$ −41·9° ⟶ −47·6° (constant) in 80 minutes} (cf. 3 : 6-anhydromannitol, $[\alpha]_D^{20}$ −29°). The solution was evaporated to dryness at 30—35° (bath-temp.)/10—12 mm., and the remaining traces of acetic acid were removed by storage *in vacuo* over phosphoric oxide and potassium hydroxide for 2 days. The syrupy residue was fractionated by extraction with water (30 c.c.), and the aqueous solution extracted with chloroform (30 c.c.). The residue remaining after the aqueous extraction was added to the chloroform solution. Evaporation of the dried ($MgSO_4$) chloroform solution gave a mobile straw-coloured syrup (0·175 g.), $[\alpha]_D^{20}$ −40·0° in ethanol : it was unchanged starting material. The aqueous solution was evaporated to dryness and the syrupy residue (1·61 g.) extracted with acetone; the undissolved material was negligible (*ca.* 5—10 mg.). The syrupy residue obtained on evaporation of the acetone solution had $[\alpha]_D^{20}$ −50·9° in ethanol and on distillation gave 4 : 5-iso*propylidene* 3 : 6-*anhydromannitol*, b. p. 125—130° (bath-temp.)/0·04 mm., n^{20} 1·4785, $[\alpha]_D^{20}$ −59·1° (*c*, 0·4 in water). On storage this substance crystallized and after recrystallization from ethyl acetate–light petroleum (b. p. 60—80°) gave the product in large colourless square plates, m. p. 83—84° (Found : C, 52·5; H, 7·7. $C_9H_{16}O_5$ requires C, 52·9; H, 7·8%).

Oxidation of 4 : 5-iso*Propylidene* 3 : 6-*Anhydromannitol*.—(a) *With periodic acid.* The procedure followed was that of Reeves (*loc. cit.*). 4 : 5-*iso*Propylidene 3 : 6-anhydromannitol (25·3 mg.) gave the formaldehyde–dimedone derivative (39·5 mg.), m. p. 185—190°, corresponding to 140% of that expected. In a series of oxidations of this *iso*propylidene derivative the dimedone derivative isolated corresponded to 115—140% of the theoretical and had an indistinct m. p. Reeves (*loc. cit.*) records anomalous results, similar to the above, encountered in periodic acid oxidations of *iso*propylidene derivatives. Presumably hydrolysis of the *iso*propylidene residue occurs under the conditions of the experiment and interferes with the estimation.

(b) *With lead tetra-acetate.* By the method described by Hockett and McClenahan (*J. Amer. Chem. Soc.*, 1939, **61**, 1667) 4 : 5-*iso*propylidene 3 : 6-anhydromannitol (103 mg.) reduced a standard solution of lead tetra-acetate in glacial acetic acid (0·0655N.) as shown :

Time (mins.)	15	35	55	90	115	215	425	900
Uptake of $Pb(OAc)_4$ (moles)...	0·208	0·416	0·566	0·717	0·792	0·924	0·943	0·962

For comparative purposes 1 : 2-*iso*propylidene D-glucofuranose (110 mg.) was oxidised under identical conditions :

Time (mins.)	18	31	65	115	155	275	415
Uptake of $Pb(OAc)_4$ (moles)...	0·249	0·364	0·632	0·785	0·834	0·958	0·97

Hydrolysis of 4 : 5-iso*Propylidene* 3 : 6-*Anhydromannitol*.—A solution of the *iso*propylidene derivative (0·2 g.) in N-sulphuric acid (10 c.c.) was boiled under reflux for 5 hours. Neutralization of the acid with barium carbonate and evaporation of the solution gave a crystalline product, m. p. 146—147° alone or on admixture with 3 : 6-anhydromannitol.

3 : 4-iso*Propylidene* 2 : 5-*Anhydro*aldehydo-D-*arabinose*.—Lead tetra-acetate (10·7 g.) was added to a solution of 4 : 5-*iso*propylidene 3 : 6-anhydromannitol (5 g.) in dry benzene (80 c.c.), and the mixture agitated mechanically for 24 hours. Addition of ether (80 c.c.) precipitated inorganic material which was filtered off. The remaining solution was freed from acid by shaking it with the minimum volume of aqueous sodium hydrogen carbonate and then filtering. The aqueous solution was extracted with benzene (3 × 100 c.c.), and the combined extracts were dried ($MgSO_4$) and evaporated to dryness, yielding a straw-coloured syrup (1·35 g., 29·4%) which strongly reduced Fehling's solution. Continuous extraction of the aqueous solution with ether for 3 days gave a further yield of product (2·85 g., 67·6%). Distillation of this product resulted in extensive polymerization of the flask residues, but 3 : 4-iso*propylidene* 2 : 5-*anhydro*aldehydo-D-*arabinose* (0·2 g.) was obtained as a thick yellow liquid, strongly reducing towards Fehling's solution, b. p. 118—124° (bath-temp.)/0·03 mm., n^{21} 1·4660, $[\alpha]_D^{20}$ −131·5° (*c*, 1·4 in benzene). Because of the tendency to polymerize (and hence to overheat during distillation, affording a discoloured product) it was not possible to obtain good analytical figures (Found : C, 54·0; H, 7·4. $C_8H_{12}O_4$ requires C, 55·8; H, 7·0%). It was sparingly soluble in water and moderately soluble in ether and benzene. In chloroform solution 3 : 4-*iso*propylidene 2 : 5-anhydro*aldehydo*-D-arabinose showed absorption at 2550 A. (ε = 170 approx.; *c*, 78·8 mg.-%).

Hydrolysis of the Foregoing Derivative.—3 : 4-*iso*Propylidene 2 : 5-anhydro-*aldehydo*-D-arabinose (3·5 g.) was heated with hydrochloric acid (60 c.c.; N.) on a boiling water-bath for 3 hours. The syrupy starting material rapidly dissolved and considerable coloration of the reaction mixture occurred. The acid was neutralized with silver carbonate and the solution evaporated to dryness after removal of the silver residues. Storage of the residue over phosphoric oxide *in vacuo* afforded a colourless hygroscopic glass (1·7 g.), $[\alpha]_D^{20}$ −22° (*c*, 0·6 in water), showing an absorption band at 2680 A. (ε = 20 approx.; *c*, 227·6 mg.-%). A similar product was isolated when sulphuric acid was used to effect hydrolysis. This product (1·6 g.) was boiled under reflux with 1·4% methanolic hydrogen chloride (25 c.c.) for 2 hours. The acid was neutralized with silver carbonate and the solution freed from silver residues by filtration through charcoal. Evaporation gave a syrupy residue, non-reducing towards Fehling's

solution, from which 2 : 5-*anhydro*-D-*arabinose dimethyl acetal* (1·27 g.) was obtained as a colourless viscous liquid, b. p. 115—120° (bath-temp.)/0·01 mm., n^{18} 1·4700, $[\alpha]_D^{20}$ −44·4° (*c*, 0·8 in methanol) (Found : MeO, 34·0. $C_7H_{14}O_5$ requires MeO, 34·8%).

1 : 2-*Diacetyl* 4 : 5-iso*Propylidene* 3 : 6-*Anhydromannitol.*—A solution of 4 : 5-*iso*propylidene 3 : 6-anhydromannitol (0·2 g.) in dry pyridine (1 c.c.) was treated with acetic anhydride (1 c.c.) at room temperature for 48 hours. The mixture was diluted with water (40 c.c.) and extracted with chloroform (5 × 25 c.c.), and the combined extracts were washed with water, dilute sodium hydrogen carbonate solution, and dried ($MgSO_4$). Evaporation afforded a syrupy residue from which the *diacetate* (0·19 g.) was obtained as a colourless viscous liquid, b. p. 115—120° (bath-temp.)/0·02 mm., n^{20} 1·4535. On storage the distillate crystallized and after recrystallization from aqueous ethanol had m. p. 42—44° and $[\alpha]_D^{20}$ −46·2° (*c*, 0·6 in chloroform) (Found : C, 54·5; H, 7·0. $C_{13}H_{20}O_7$ requires C, 54·2; H, 6·9%).

1 : 2-*Di*-p-*nitrobenzoyl* 4 : 5-iso*Propylidene* 3 : 6-*Anhydromannitol.*—*p*-Nitrobenzoyl chloride (2·2 mols., 0·4 g.) was added to a solution of 4 : 5-*iso*propylidene 3 : 6-anhydromannitol (0·2 g.) in dry pyridine (2 c.c.), and the mixture set aside at room temperature for 10 hours. On addition of water a syrupy product separated which crystallized on trituration. Recrystallization from acetone–water–methanol gave the *di*-p-*nitrobenzoate* as elongated prisms, m. p. 169—170°, $[\alpha]_D^{20}$ −29·6° (*c*, 0·4 in chloroform) (Found : C, 54·7; H, 4·2. $C_{33}H_{32}O_{11}N_2$ requires C, 55·0; H, 4·4%).

1 : 2-*Dimethanesulphonyl* 4 : 5-iso*Propylidene* 3 : 6-*Anhydromannitol.*—4 : 5-*iso*Propylidene 3 : 6-anhydromannitol (0·55 g.), in dry pyridine (3 c.c.), was treated with methanesulphonyl chloride (2·5 mols., 0·75 g.) at room temperature for 2·5 hours. The mixture was diluted with water (150 c.c.) and extracted with chloroform (2 × 100 c.c.), and the combined extracts were washed successively with water (twice), 0·5N-hydrochloric acid (thrice; total vol., 250 c.c.), and dilute sodium hydrogen carbonate solution, and dried ($MgSO_4$). Evaporation yielded a syrupy residue which crystallized on trituration with ethanol. Recrystallization from aqueous ethanol afforded the *dimethanesulphonyl* derivative (0·46 g.) as colourless needles, m. p. 85—88°, $[\alpha]_D^{20}$ −46·7° [*c*, 0·4 in chloroform–carbon tetrachloride (5 : 1)] (Found : C, 36·8; H, 5·7. $C_{11}H_{20}O_9S_2$ requires C, 36·7; H, 5·6%).

1 : 2-*Ditoluene*-p-*sulphonyl* 4 : 5-iso*Propylidene* 3 : 6-*Anhydromannitol.*—A solution of 4 : 5-*iso*propylidene 3 : 6-anhydromannitol (0·1 g.) in dry pyridine (0·5 c.c.) was treated with toluene-*p*-sulphonyl chloride (2·4 mols., 0·26 g.) at room temperature for 48 hours. Dilution with water caused separation of the *ditoluene*-p-*sulphonate* which after recrystallisation from ethanol was obtained as colourless needles, m. p. 125—126°, $[\alpha]_D^{20}$ −31·7° (*c*, 0·9 in chloroform) (Found : C, 53·7; H, 6·0. $C_{33}H_{38}O_9S_2,C_2H_5{\cdot}OH$ requires C, 53·8; H, 6·1%).

Iodine-exchange Experiments.—The iodine-exchange experiments were carried out under strictly comparable conditions. Solutions containing equimolecular proportions of the above methanesulphonyl or toluene-*p*-sulphonyl derivatives and sodium iodide in equal volumes of acetone were heated in sealed tubes at identical temperatures. When 1 : 2-dimethanesulphonyl 4 : 5-*iso*propylidene 3 : 6-anhydromannitol (250 mg.) was heated in acetone (10 c.c.) with sodium iodide (2·2 mols., 250 mg.), sodium methanesulphonate (70 mg.) was precipitated, corresponding to 0·866 mole of methanesulphonyloxy-group. 4 : 5-*iso*Propylidene 1 : 2-ditoluene-*p*-sulphonyl 3 : 6-anhydromannitol (355 mg.), treated as above, gave sodium toluene-*p*-sulphonate (130 mg.) corresponding to 0·966 mole of toluene-*p*-sulphonyloxy-residue. Both tubes were heated at 100—105° for 1·5 hours and in each case there was extensive liberation of iodine (cf. Foster, Overend, Stacey, and Wiggins, *loc. cit.*). The salts were collected in a sintered-glass funnel, washed well with dry acetone, and dried at 130° for 20 minutes before being weighed.

4 : 5-iso*Propylidene* 3 : 6-*Anhydromannitoleen.*—A solution of the ditoluene-*p*-sulphonyl derivative (3·0 g.) in dry acetone (25 c.c.) containing sodium iodide (3·0 g.) was heated in a sealed tube at 125—130° for 4 hours. Sodium toluene-*p*-sulphonate (2·13 g., 1·836 moles) was precipitated, and iodine liberated. After removal of the precipitated salt, the filtrate was diluted with chloroform (75 c.c.) and washed with aqueous sodium thiosulphate solution. The chloroform solution was dried ($MgSO_4$) and evaporated, and the syrupy residue distilled. 4 : 5-iso*Propylidene* 3 : 6-*anhydromannitoleen* (0·7 g.) was obtained as a colourless mobile liquid, b. p. 65—75° (bath-temp.)/0·05 mm., which rapidly crystallised on cooling and then had m. p. 23—24°, $[\alpha]_D^{17}$ +87·5° (*c*, 0·9 in methanol) (Found : C, 61·9; H, 8·5. $C_9H_{14}O_4$ requires C, 63·5; H, 8·3%).

4 : 5-iso*Propylidene* 3 : 6-*Anhydro*-1 : 2-*dideoxymannitol.*—4 : 5-*iso*Propylidene 3 : 6-anhydromannitoleen (0·65 g.), in methanol (40 c.c.), was shaken vigorously at room temperature in an atmosphere of hydrogen at a slight over-pressure in the presence of platinum oxide (50 mg.). Hydrogen (95 c.c.) was rapidly absorbed, and after removal of the catalyst and evaporation of the solvent a straw-coloured syrup was isolated from which 4 : 5-iso*propylidene* 3 : 6-*anhydro*-1 : 2-*dideoxymannitol* (0·45 g.) was obtained as a colourless mobile liquid, b. p. 50—55° (bath-temp.)/0·2 mm., n^{17} 1·4330, $[\alpha]_D^{20}$ −49·1 (*c*, 0·6 in methanol) (Found : C, 61·5; H, 9·3. $C_9H_{14}O_3$ requires C, 62·8; H, 9·2%). Both this compound and its precursor were extremely hygroscopic and it was not possible to obtain good analytical data for them.

The authors thank Professor M. Stacey, F.R.S., for his general interest in this investigation and Messrs. Imperial Chemical Industries Limited for a grant towards the expenses. One of them (A. B. F.) is grateful to the Brewing Industry Research Foundation for financial assistance during part of the work.

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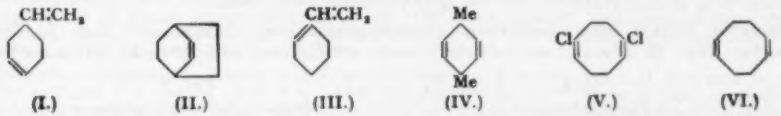
146. *The Formation of* trans-1 : 2-*Divinylcyclobutane from Butadiene.*

By Hugh W. B. Reed.

About 5% of *trans*-1 : 2-divinyl*cyclo*butane has been shown to be present in the products of the thermal dimerisation of butadiene, with probably a trace of octa-1 : 3 : 7-triene.

The thermal dimerisation of buta-1 : 3-diene was first investigated by Lebedev (*J. Russ. Phys. Chem. Soc.*, 1910, **42**, 949) who established, contemporaneously with Hoffmann and Tank (*Z. angew. Chem.*, 1912, **25**, 1465), the structural formula of the product as 4-vinyl*cyclo*hexene (I) (see also Lebedev and Skavvonskaya, *J. Russ. Phys. Chem. Soc.*, 1911, **43**, 1124; Lebedev,



(I.) (II.) (III.) (IV.) (V.) (VI.)

ibid., 1913, **45**, 1249). Since 1930, numerous workers have described the use of various catalysts and conditions giving several other ill-defined dimeric products besides 4-vinyl*cyclo*hexene. Vaughan (*J. Amer. Chem. Soc.*, 1932, **54**, 3866) claimed the preparation of (II), but it seems very likely that this was, in fact, 4-vinyl*cyclo*hexene itself. Lebedev and Sergienko (*J. Gen. Chem. U.S.S.R.*, 1935, **5**, 1829) obtained evidence for the existence of a dimer boiling higher than 4-vinyl*cyclo*hexene, and ascribed to it the conjugated structure, 1-vinyl*cyclo*hexene (III). Slobodin (*ibid.*, p. 1415) claimed the formation of the 1 : 4-dihydro-*p*-xylene (IV) and isomers of it; more evidence for this has recently been given (Slobodin and Rachinsky, *ibid.*, 1947, **17**, 374; Slobodin, Rachinsky, and Shokov, *ibid.*, 1948, **18**, 1545), but the yields appear to be very small.

After Brown, Rose, and Simonsen's observation (*J.*, 1944, 101) that 2-chlorobutadiene dimerises on storage to give a product containing a *cyclo*octadiene derivative which is now recognised to be 1 : 6-dichloro*cyclo*octa-1 : 5-diene (V) (Cope and Schmitz, *J. Amer. Chem. Soc.*, 1950, **72**, 3056), Foster and Schreiber (*ibid.*, 1948, **70**, 2303) and Ziegler (*Angew. Chem.* 1947, *A.*, **59**, 177) demonstrated the presence of a *cyclo*octadiene in the higher-boiling material remaining after the removal of the 4-vinyl*cyclo*hexene. Characterisation of this compound as the stable *cis-cis-cyclo*octa-1 : 5-diene (VI) has been recently achieved by Ziegler and Wilms (*Annalen*, 1950, **567**, 1).

The non-catalytic thermal dimerisation of butadiene has now been shown to yield another product, identified as substantially *trans*-1 : 2-divinyl*cyclo*butane (VII). This appeared at about 110° during the distillation of the products before the 4-vinyl*cyclo*hexene and was isolated by high-efficiency fractionation of the bulked foreruns from a number of experiments. It was estimated to amount to 4—5% of the 4-vinyl*cyclo*hexene.

The presence of two ethylenic linkages was indicated by absorption of two molecules of bromine to give a liquid tetrabromide and two molecules of hydrogen to yield a fully saturated hydrocarbon, evidently *trans*-1 : 2-diethyl*cyclo*butane.

Physical constants of butadiene dimers and their hydrogenated derivatives.

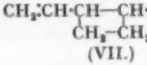
trans-1 : 2-Divinyl*cyclo*butane [1]	b. p. 112—113°	n_D^{20} 1·4451	d_{20}^{20} 0·7831
4-Vinyl*cyclo*hexene [1]	b. p. 131°	n_D^{20} 1·4655	d_{20}^{20} 0·8309
*cis-cis-cyclo*Octa-1 : 5-diene [2]	b. p. 151°	$n_{H_\alpha}^{20}$ 1·4936	d_4^{20} 0·8811
,, ,, [3]	b. p. 51—52°/25 mm.	n_D^{20} 1·4910	d_4^{20} 0·8760
trans-1 : 2-Diethyl*cyclo*butane [1]	b. p. 115·5°	n_D^{20} 1·4128	—
Ethyl*cyclo*hexane [1]	b. p. 131°	n_D^{20} 1·4329	—
*cyclo*Octane [2]	b. p. 150°	$n_{H_\alpha}^{20}$ 1·4587	d_4^{20} 0·8358

[1] Reed, this work. [2] Ziegler and Wilms, *loc. cit.* [3] Cope, Stevens, and Hochstein, *J. Amer. Chem. Soc.*, 1950, **72**, 2512.

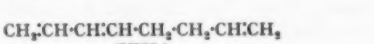
The infra-red spectrum (Fig. 2), clearly different from that of 4-vinyl*cyclo*hexene (Fig. 1) showing that none of the latter was present, was characterised by the strong absorption at 10·1 and 11μ., typical of the vinyl group. Absence of absorption bands characteristic of other

types of ethylenic linkage (Thomson, *J.*, 1948, 328) indicated the probability that both double bonds were present as exocyclic vinyl groups.

Ozonolysis of the dimer in methyl acetate at −40° gave *trans-cyclo*butane-1 : 2-dicarboxylic acid, m. p. 131° (Fuson *et al.*, *J. Amer. Chem. Soc.*, 1929, **51**, 1536; 1934, **56**, 1774; Buchman, Reims, and Schlatter, *ibid.*, 1942, **64**, 2692) (diphenacyl and di-*p*-bromophenacyl ester). Further examination of the ozonolysis products after removal of the *trans-cyclo*butane-1 : 2-dicarboxylic acid led to the isolation of a small amount of succinic acid (diphenacyl and di-*p*-bromophenacyl esters); no isomeric *cyclo*butanedicarboxylic acid was found. Although the high volatility of the hydrocarbon and its ready autoxidation resulted in some loss during ozonolysis, it is concluded that it consisted mainly of the *cyclo*butane derivative (VII) with probably a small amount of octa-1 : 3 : 7-triene (VIII).



(VII.)



(VIII.)

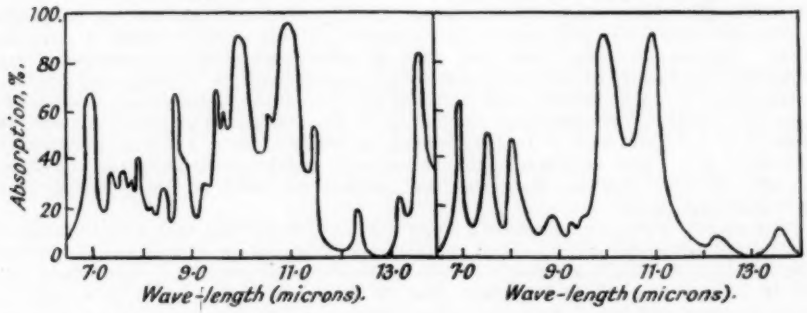
Recently, certain highly substituted chlorofluoroethylenes (Henne and Ruh, *J. Amer. Chem. Soc.*, 1947, **69**, 279) and acrylonitrile (Coyner and Hillman, *ibid.*, 1949, **71**, 324) have been

FIG. 1.

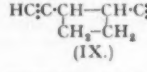
4-*Vinyl*cyclo*hexene*.

FIG. 2.

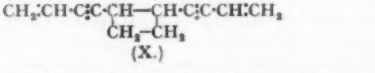
trans-1 : 2-*Divinyl*cyclo*butane*.



shown to yield *cyclo*butane derivatives by head-to-head, tail-to-tail dimerisation on heating. Dykstra (*ibid.*, 1934, **56**, 1625) and Cupary and Carothers (*ibid.*, p. 1167) had assigned *cyclo*butane structures (IX) and (X) to the dimers formed on heating of vinylacetylene and divinylacetylene respectively.



(IX.)



(X.)

These formulæ have been the subject of much criticism by Bergmann (*Trans. Faraday Soc.*, 1939, **35**, 1025; "The Chemistry of Acetylene Compounds," Interscience, New York, 1948, p. 81), but comparison of the physical constants of the octahydro-derivative of (IX) (b. p. *ca.* 120°, n_D^{20} 1·4270) with hydrogenated *trans*-1 : 2-divinyl*cyclo*butane, together with Cupary and Carothers's chemical evidence (*loc. cit.*), indicates that the vinyl- and divinyl-acetylene dimers undoubtedly contain at least a considerable proportion of compounds (IX) and (X) respectively.

EXPERIMENTAL.

Infra-red absorption spectra were determined with a Grubb Parsons spectrometer, the pure liquids being used in a cell of 30—50-μ. thickness.

trans-1 : 2-*Divinyl*cyclo*butane from Butadiene*.—Butadiene was heated in an autoclave at 150° for 18 hours under a pressure adjusted to 100 atmospheres with nitrogen. Oxygen was carefully excluded, and 3% of quinol used to inhibit polymerisation. The products were distilled in a 60-plate high-efficiency still and the initial fraction, b. p. <131°, was reserved. A number of these foreruns were bulked and redistilled in the same still. trans-1 : 2-*Divinyl*cyclo*butane*, b. p. 112—113°, was obtained (for physical constants see table) (Found: C, 88·9; H, 11·2%; Br no., 300. C_8H_{12} requires C, 88·9; H, 11·1%; Br no., 297).

trans-1 : 2-*Diethyl*cyclo*butane*.—The dimer (8·04 g.) was hydrogenated at room temperature and pressure in acetic acid (40 c.c.) in the presence of pre-reduced Adams's platinum oxide catalyst; 3510 c.c.

were absorbed (Calc. for two moles of hydrogen, 3570 c.c.). Filtercel was then added, and the catalyst removed by filtration and washed with ether. Ether was added to the filtrate, the acetic acid washed out, and the ethereal solution distilled, to give trans-1 : 2-*diethyl*cyclo*butane* (5·8 g.), b. p. 115·5° (see table) (Found : C, 85·7; H, 14·4. C_8H_{16} requires C, 85·7; H, 14·3%).

Ozonolysis of trans-1 : 2-*Divinyl*cyclo*butane.*—*trans*-1 : 2-Divinyl*cyclo*butane (2·54 g.) in methyl acetate (50 c.c.) was ozonised at −40°. After completion of the ozonisation, the solvent was removed *in vacuo*, and the ozonide decomposed by warming it on a water-bath with 40 c.c. of water and 3 c.c. of 30% hydrogen peroxide. After final heating of the solution for 30 minutes, the water was removed *in vacuo*. The clear oil (2·3 g.) remaining solidified completely on storage and was then taken up in ethyl acetate, and a little insoluble polymeric material removed. Benzene was added, and a crystalline solid (1·04 g.), m. p. 123—128°, obtained; recrystallisation from benzene–ethyl acetate gave pure *trans-cyclo*butane-1 : 2-dicarboxylic acid, needles, m. p. 131° (Found : C, 50·0; H, 5·6%; equiv., 72. Calc. for $C_6H_8O_4$: C, 50·0; H, 5·5%; equiv., 72). It gave the *di*-p-*bromophenacyl* ester, needles (from alcohol), m. p. 158° (Found : C, 49·1; H, 3·6. $C_{32}H_{18}O_6Br_2$ requires C, 49·1; H, 3·35%), and the *di-phenacyl* ester, needles (from alcohol), m. p. 98° (Found : C, 69·5; H, 5·4. $C_{32}H_{30}O_6$ requires C, 69·5; H, 5·3%). From the filtrate from the initial *trans-cyclo*butane-1 : 2-dicarboxylic acid, a further 0·5 g. of impure acid (m. p. 120—125°) was obtained (yielding only the diphenacyl ester, m. p. 98° above). Finally, 74 mg. of impure succinic acid, m. p. 175—178°, were obtained [di-*p*-bromophenacyl ester, plates (from methyl ethyl ketone), m. p. and mixed m. p. 211°, and diphenacyl ester, needles (from alcohol), m. p. and mixed m. p. 151°].

Authentic cyclo*Butanedicarboxylic Acids.*—*cis-cyclo*Butane-1 : 2-dicarboxylic acid, prepared by the method of Fuson *et al.* (*loc. cit.*), had m. p. 139·5° and gave the *di*-p-*bromophenacyl* ester, plates (from ethanol–acetone), m. p. 153° (Found : C, 49·2; H, 3·5%) and the *di-phenacyl* ester, needles (from alcohol), m. p. 113° (Found : C, 69·4; H, 5·3%). *trans-cyclo*Butane-1 : 2-dicarboxylic acid, prepared by isomerisation of the *cis*-acid in concentrated hydrochloric acid at 190°, was identical with the sample prepared above, as were the corresponding derivatives. *trans-cyclo*Butane-1 : 3-dicarboxylic acid, m. p. 174° (Haworth and Perkin, *J.*, 1898, **73**, 336), gave the *di*-p-*bromophenacyl* ester, needles (from ethanol), m. p. 122° (on heating from room temperature), m. p. 129° (on reheating after initial solidification) (Found : C, 49·2; H, 3·5%), and the *di-phenacyl* ester, needles (from ethanol), m. p. 100° (Found : C, 69·5; H, 5·3%).

IMPERIAL CHEMICAL INDUSTRIES LIMITED,
RESEARCH DEPARTMENT, BILLINGHAM, CO. DURHAM. [*Received, September 20th*, 1950.]

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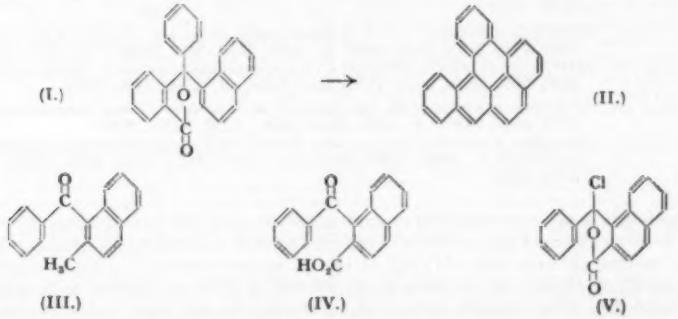
147. *Aromatic Hydrocarbons. Part LIX.* 1 : 2-3 : 4-*Dibenzpyrene.*

By E. CLAR and D. G. STEWART.

1 : 2-3 : 4-Dibenzpyrene, a strongly carcinogenic hydrocarbon, was synthesised by an unambiguous method, 9-phenyl-1 : 2-benzanthracene being used as an intermediate stage. It was found to be identical with a hydrocarbon obtained by an earlier ambiguous synthesis. An attempt to synthesise oxygen-containing derivatives of 1 : 2-3 : 4-dibenzpyrene is described.

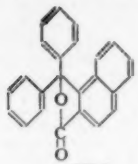
1 : 2-3 : 4-DIBENZPYRENE (II), which has been shown to be strongly carcinogenic (Bachmann, Cook, Dansi, de Worms, Hewett, and Robinson, *Proc. Roy. Soc., B*, 1937, **123**, 350; Cook and Kennaway, *Amer. J. Cancer*, 1938, **33**, 53), was obtained directly from α-phenyl-α-1-naphthyl-



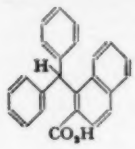
phthalide (I) and also indirectly (Clar, *Ber.*, 1930, **63**, 112). However, this synthesis could also yield the isomeric 1 : 2-benzperylene and although considerable support in favour of the

dibenzpyrene formula was forthcoming from spectrographical investigations, a direct proof by an unambiguous synthesis was desirable.

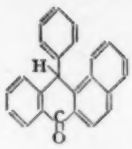
The new synthesis of (II) starts with 1-benzoyl-2-methylnaphthalene (III), which is oxidised to the acid (IV) with aqueous selenious acid under pressure at 250°. The chloro-compound (V) is obtained from (IV) by means of thionyl chloride, and Friedel–Crafts reaction of this with benzene gives the lactone (VI). Unlike the isomeric lactone (I), the former cannot be condensed



(VI.)



(VII.)



(VIII.)

(IX.)

to dibenzpyrene in a sodium chloride–aluminium chloride melt at 140°, and the starting material is recovered unchanged. The carbonyl group obviously deactivates the naphthalene ring.

Reduction of the lactone (VI) with alcoholic potassium hydroxide and zinc dust gives the acid (VII), which after treatment with sulphuric acid at room temperature yields

FIG. 1. FIG. 2.

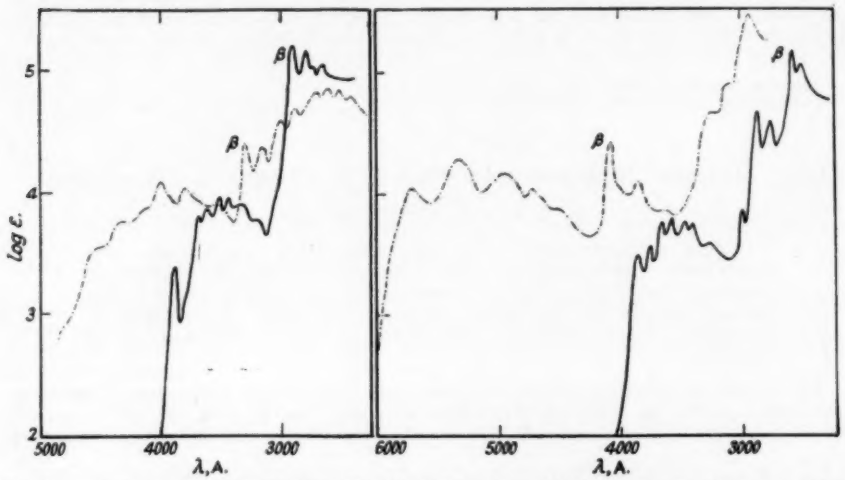


FIG. 1. — · — · — *Absorption spectrum of* 1 : 2-3 : 4-*dibenzpyrene in alcohol. Band maxima in* A.: 4540, 4260, 4120, 4010, 3790, 3590: β; 3305, 3150, 3010, 2890, 2710, 2610, 2530, 2400.

———— *Absorption spectrum of* 9-*phenyl*-1 : 2-*benzanthracene in alcohol. Band maxima in* A.: 3890, 3680, 3620, 3520, 3450, 3350, 3200: β; 2900, 2795, 2690.

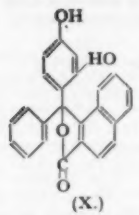
FIG. 2. — · — · — *Absorption spectrum of the red hydrocarbon in benzene. Band maxima in* A.: 5710, 5330, 4940, 4630: β; 4080, 3850, 3630; 3230, 3090; 2925.

———— *Absorption spectrum of octa- or deca-hydro*-1 : 2-3 : 4-*dibenzpyrene in alcohol. Band maxima in* A.: 3865, 3760, 3660; 3580, 3480, 3410, 3260; 3000; 2875, 2775: β; 2595, 2520.

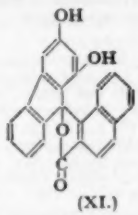
(VIII). Since this compound dissolves in cold aqueous alkali and is oxidisable by molecular oxygen, it must be assumed that it exists in the enol form to a considerable extent. A sodium chloride–aluminium chloride melt of (VIII) at 140° gives poor yields of 1 : 2-3 : 4-dibenzpyrene (II). This *peri*-ring closure can be more easily effected if (VIII) is reduced to 9-phenyl-1 : 2-benzanthracene (IX) with alcoholic potassium hydroxide and zinc dust, and this then treated with aluminium chloride in boiling benzene. The 1 : 2-3 : 4-dibenzpyrene thus obtained and purified by chromatography is identical with the hydrocarbon previously synthesised (Clar,

loc. cit.). Its absorption spectrum (Fig. 1) shows the expected striking difference from that of the formally similar 9-phenyl-1 : 2-benzanthracene (IX).

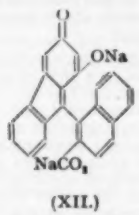
The chromatographic purification of the crude dibenzpyrene also gives two other hydrocarbons in small yield, one of which is deep red, the other colourless. Their absorption spectra are reproduced in Fig. 2. The β-band at 2595 A. of the colourless hydrocarbon, which is readily volatile in a vacuum, requires a conjugated system of at least 14 π-electrons as in phenanthrene or anthracene, according to the anellation principle. The analytical figures indicate an



(X.)



(XI.)



(XII.)

octahydro- or decahydro-1 : 2-3 : 4-dibenzpyrene, and it is obvious that this hydrocarbon acts as a hydrogen acceptor during the condensation.

To obtain an oxygen-containing dibenzpyrene, (V) was condensed with resorcinol in boiling glacial acetic acid. The melt of the product (X) with sodium chloride–aluminium chloride at 140°, due to an incomplete ring closure, yields a compound which according to the analytical data, and taking into account the resistance of the naphthalene complex to *peri*-condensation, probably has the structure (XI). It gives a pale-yellow solution in hot sodium carbonate solution and a deep red-brown one in cold sodium hydroxide solution. In the latter case the quinoid salt (XII) is obviously formed.

Experimental.

(All m. p.s are uncorrected and taken in evacuated capillaries.)

1-*Benzoyl-2-methylnaphthalene* (III).—This ketone was prepared from 2-methylnaphthalene (75 g.) and benzoyl chloride (75 g.) in benzene (75 g.), with aluminium chloride (75 g.). After the usual decomposition the oil was distilled in a vacuum and gave a 85% yield of crystalline material.

1-*Benzoyl-2-naphthoic Acid* (IV).—1-Benzoyl-2-methylnaphthalene (10 g.), selenium dioxide (17·5 g.) and water (10 g.) were heated for 10 hours at 250° in a sealed glass-tube. The brown solid obtained was washed with water and dissolved in boiling dilute sodium hydroxide solution. After being boiled with charcoal the hot solution was filtered and, on cooling, the sodium salt of the acid crystallised in plates, which were redissolved in hot water and acidified with hydrochloric acid. The *acid* thus obtained was recrystallised from xylene and yielded colourless needles, m. p. 220—221° (Found : C, 78·5; H, 4·5. $C_{18}H_{12}O_3$ requires C, 78·2; H, 4·4%). Another portion of acid was obtained from the alkaline mother-liquors, bringing the total yield up to 76%. The acid dissolved readily in concentrated sulphuric acid to give a dark-green solution.

1-(α-*Hydroxydiphenylmethyl*)-2-*naphthoic Acid Lactone* (VI).—The chloride (V) (24 g.), obtained by boiling the acid with thionyl chloride (100 g.) and removing the excess of the latter in a vacuum, was dissolved in benzene (200 g.). Aluminium chloride (30 g.) was added with ice-cooling, and next morning the temperature was raised to 50° for a few minutes. The usual decomposition yielded a light-brown benzene layer, from which colourless needles (11 g.) separated on cooling. Recrystallisation from acetic acid gave crystals (11 g.), m. p. 236—237° (Found : C, 85·0; H, 4·9. $C_{24}H_{16}O_2$ requires C, 85·7; H, 4·8%). Another portion (10 g.) was obtained by concentration of the benzene mother-liquors, the total yield being 77%. The *lactone* dissolved in concentrated sulphuric acid to a yellowish-green solution.

1-*Diphenylmethyl-2-naphthoic Acid* (VII).—The lactone (7·5 g.) was dissolved by boiling it with 20% alcoholic potassium hydroxide (150 c.c.) for 2 hours. Zinc dust (30 g.), activated with copper, was added in 5-g. portions during 2½ hours, and the mixture refluxed for a further 3 hours. The hot solution was filtered and the excess of zinc dust extracted with boiling dilute sodium hydroxide. The combined filtrates were diluted with water and acidified with hydrochloric acid. The *acid* yielded colourless crystals (7 g.), m. p. 227—228°, after recrystallisation from xylene (Found : C, 84·7; H, 5·6. $C_{24}H_{18}O_2$ requires C, 85·2; H, 5·4%).

9-*Phenyl*-1 : 2-*benzanthrone* (VIII).—The acid (VII) (6 g.) was powdered and dissolved in concentrated sulphuric acid (250 c.c.) at 10°. The solution was yellow-orange at first but after a few minutes it darkened to a deep orange-brown. The temperature was not allowed to rise above 18°. After precipitation with iced water, the solid was filtered off and treated with boiling dilute ammonia solution. The greyish-white residue was recrystallised from acetic acid and gave colourless crystals (5 g.), m. p. 185—187°, of the *benzanthrone*, which on exposure to air and light became tinged violet. The analytical

figures are therefore not quite satisfactory (Found: C, 88·3; H, 5·1. $C_{24}H_{16}O$ requires C, 90·0; H, 5·0%).

9-*Phenyl*-1 : 2-*benzanthracene* (IX).—9-Phenyl-1 : 2-benzanthrone (2·5 g.) was added to a boiling suspension of zinc dust (10 g.), activated with copper, in 20% alcoholic potassium hydroxide (100 c.c.) and the mixture heated for 8 hours on a water-bath. The solution lost its initial deep-yellow colour. The excess of zinc dust was filtered off whilst hot, and thoroughly washed with boiling alcohol. The combined filtrates were concentrated to 75 c.c.; on cooling, light-brownish needles crystallised. A second crop was obtained after dilution of the mother-liquors with water. Recrystallisation from alcohol yielded colourless silky needles (2·2 g.), m. p. 154—155° (Found: C, 94·8; H, 5·4. $C_{24}H_{16}$ requires C, 94·7; H, 5·3%). The *compound* dissolved in concentrated sulphuric acid to a deep cherry-red solution which became light-brown on being kept. The solution in benzene showed a blue fluorescence.

1 : 2-3 : 4-*Dibenzpyrene from* 9-*Phenyl*-1 : 2-*benzanthrone*.—9-Phenyl-1 : 2-benzanthrone (VIII) (1 g.) was added to a melt of sodium chloride (1·2 g.)–aluminium chloride (6 g.) at 140°, and this temperature maintained for 1 hour. The dark-brown melt was poured into dilute hydrochloric acid, and the solid washed thoroughly with hot water. The dry substance was dissolved in anhydrous benzene (50 c.c.) and chromatographed on activated alumina (60 g.; 50 cm. high column). The first eluate with benzene yielded a very small quantity of crystals melting unsharply at 152—155°. The main fraction, a bright yellowish-green solution with a brilliant green fluorescence, gave, after concentration to small volume and addition of acetic acid, a small quantity of yellow needles, m. p. 221—225°. The mixed m. p. with a previous sample of 1 : 2-3 : 4-dibenzpyrene (m. p. 226—227°) was 223—226°. The needles, like the previous sample, gave a violet-red solution in concentrated sulphuric acid, which changed to green on being kept.

1 : 2-3 : 4-*Dibenzpyrene from* 9-*Phenyl*-1 : 2-*benzanthracene*.—9-Phenyl-1 : 2-benzanthracene (IX) (0·75 g.) and powdered aluminium chloride (5 g.) were heated in benzene (75 c.c.) on a water-bath. Almost at once a deep-violet colour developed which quickly changed to dark brown and then to a deep red. After decomposition with dilute hydrochloric acid, the benzene layer was washed and dried ($CaCl_2$). The result of the chromatographic separation was found to depend on the period of condensation.

A condensation product in benzene which was obtained by 3-hours heating with aluminium chloride was adsorbed on alumina and developed with light petroleum (40—60°)–benzene. The first eluate (*A*) was colourless with a violet-blue fluorescence, the second (*B*) was yellow with a green fluorescence, and a brown band remained on the column. If the condensation was carried out for 5—10 minutes only, a deep-red eluate (*C*) was obtained following the yellow fraction (*B*). In addition a small green zone developed below the brown band but these were not investigated.

In every case 1 : 2-3 : 4-dibenzpyrene was obtained from the yellow solution (*B*) by concentration and recrystallisation from a small quantity of benzene. It melted at 224—226° and had a melting point of 224—226° when mixed with a previous sample of dibenzpyrene. The dibenzpyrene prepared by this new method was identical with that obtained from earlier syntheses in its fluorescence in solution and in the solid state, in the colour of its solution in sulphuric acid, and in its absorption spectrum.

Octahydro- or Decahydro-1 : 2-3 : 4-*dibenzpyrene*.—Fraction (*A*) was concentrated to a small volume and colourless crystals were obtained, which, after recrystallisation from alcohol, melted at 231—232°. They sublimed readily in a vacuum and dissolved in concentrated sulphuric acid to give a yellow solution, which, on being kept, changed to green (Found: C, 92·4, 92·8; H, 7·6, 7·5. $C_{24}H_{22}$ requires C, 92·8; H, 7·1. $C_{24}H_{24}$ requires C, 92·3; H, 7·7%).

The red condensation product was obtained by concentration of the red fraction (*C*) and recrystallisation from benzene. The deep-red needles (m. p. 213—214°) which fluoresced orange in benzene gave a red-brown solution in concentrated sulphuric acid which changed to violet on being kept. The absorption spectrum is shown in Fig. 2. The amount of hydrocarbon obtained was not sufficient to permit establishment of the exact composition.

1-(*α-Hydroxy*-2 : 4-*dihydroxydiphenylmethyl*)-2-*naphthoic Acid Lactone* (X).—1-(α-Chloro-α-hydroxybenzyl)-2-naphthoic acid lactone (V) (5 g.) and resorcinol (5 g.) were dissolved in glacial acetic acid (50 c.c.) and heated to boiling. Hydrogen chloride was evolved copiously, and the dark-brown solution became paler. A heavy deposit of crystals was obtained and more was isolated from the mother liquors by steam-distillation. Recrystallisation from acetic acid yielded colourless crystals (5 g.) which gave an orange-red melt at 289—290° and dissolved in concentrated sulphuric acid to a deep-red solution which rapidly became pale yellow (Found: C, 78·3; H, 4·5. $C_{24}H_{14}O_4$ requires C, 78·3; H, 4·4%).

1-(1 : 3 : 9-*Trihydroxy*-9-*fluorenyl*)-2-*naphthoic Acid Lactone* (XI).—Sodium chloride (4 g.) and powdered aluminium chloride (17 g.) were fused at 140°, and (X) (2 g.) was added. After 1 hour the melt was decomposed with dilute hydrochloric acid, and the dark-brown precipitate was filtered off and washed with hot water. After repeated crystallisation from dilute acetic acid (charcoal) and xylene–acetic acid, light brownish-yellow plates, m. p. 322—324°, were obtained (Found: C, 78·7; H, 4·1. $C_{24}H_{14}O_4$ requires C, 78·7; H, 3·9%). These gave a yellow solution in concentrated sulphuric acid which became pale violet and then colourless on being kept. The lactone dissolved in boiling sodium carbonate to a pale yellow solution, and in cold sodium hydroxide to a deep red-brown one.

UNIVERSITY OF GLASGOW. [*Received, October 25th*, 1950.]

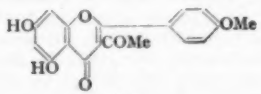
148. *The Structures of Buddleoflavonoloside (Linarin) and of Buddleoflavonol (Acacetin).*

By Wilson Baker, R. Hemming, and W. D. Ollis.

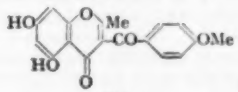
Buddleoflavonoloside, a glycoside isolated from *Buddleia variabilis*, gives L-rhamnose, D-glucose, and acacetin (III) on acid hydrolysis. This aglycone had been previously incorrectly regarded as 3-acetylacacetin. Hydrolysis of the methylated glycoside gave 5-methylacacetin, 2 : 3 : 4-trimethyl L-rhamnose, and 2 : 3 : 4-trimethyl D-glucose, thus establishing the structure of buddleoflavonoloside as 7-rutinosylacacetin (VII), a glycoside which had previously been found to occur in toad flax, *Linaria vulgaris*, and had been termed linarin.

Yü (*Bull. Soc. Chim. biol.*, 1933, **15**, 483) isolated from the leaves, buds, and flowers of the shrub, *Buddleia variabilis* Hemsl. var. grandiflora, a glycoside, buddleoflavonoloside, for which the formula $C_{30}H_{34}O_{15}$ was proposed. Hydrolysis of this glycoside was reported to give an aglycone, buddleoflavonol, $C_{15}H_{14}O_6$, L-rhamnose, and D-glucose. The position of attachment and the structure of the disaccharide residue were not determined.

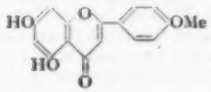
According to Yü, buddleoflavonol is 3-acetyl-5 : 7-dihydroxy-4′-methoxyflavone (3-acetylacacetin) (I), but it occurred to us that if his observations were correct the alternative, isomeric structure, 3-anisoyl-5 : 7-dihydroxy-2-methylchromone (II) was equally possible on the evidence available (cf. Baker, *J.*, 1933, 1381). Recently, Baker and Butt (*J.*, 1949, 2142; see also Baker and Glockling, *J.*, 1950, 2759) have shown that it is possible to differentiate between such isomeric compounds by reaction with benzylamine, and it was, therefore, considered opportune to reinvestigate the structures of buddleoflavonol and of buddleoflavonoloside.



(I.)



(II.)



(III.)

We have found that a glycoside, obviously identical with that described by Yü, can be easily extracted from the leaves, flowers, or buds of *Buddleia variabilis* and gives a well-crystalline aglycone on acid hydrolysis. This phenolic aglycone was found to be represented by the formula $C_{15}H_7O_2(OH)_3(OMe)$; it gave a reddish-brown ferric chloride reaction, was readily converted into diacetyl and dimethyl derivatives, and on demethylation yielded a trihydroxy-compound, characterised as its triacetyl derivative. Comparison of the properties of the aglycone and its derivatives with those of acacetin (5 : 7-dihydroxy-4′-methoxyflavone) (III) and its derivatives (see Table I) showed undoubted identity.

Table I.

	Buddleoflavonol. M. p.	Acacetin. M. p.
	263° [a]; 265° [b]	263° [a]; 261° [c]
Diacetyl derivative	204° [a]	204° [a]; 203° [c]
Dimethyl derivative	156° [a]	156° [d]
Demethyl derivative	346—348° [a]	347° [d]
Triacetyl demethyl derivative	182° [a]	181—182° [d]

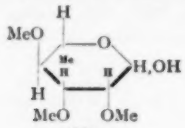
[a] This paper. [b] Yü (*loc. cit.*). [c] Robinson and Venkataraman (*J.*, 1926, 2348). [d] Czajkowski, Kostanecki, and Tambor (*Ber.*, 1900, **33**, 1991).

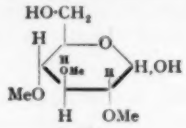
Yü states that the aglycone gives a positive iodoform test, but we have been unable to confirm this. He also claims that alkaline hydrolysis of the aglycone gave acetone, which was detected by colour tests. We were unable to detect the liberation of acetone during the alkaline hydrolysis of the aglycone when the volatile products were passed into an acid solution of 2 : 4-dinitrophenylhydrazine.

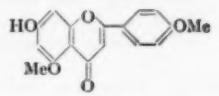
The sugars formed by hydrolysis of buddleoflavonoloside were identified as L-rhamnose and D-glucose, which were separated by partition chromatography on a column of hydrocellulose, using *n*-butanol–ethanol–water as the mobile phase. With the aid of an automatic receiver changer (Hough, Jones, and Wadman, *J.*, 1949, 2511) the eluate was separated into two portions, one containing L-rhamnose, characterised as its *N*-benzoylhydrazone, and the other containing D-glucose, characterised as its β-penta-acetate. Buddleoflavonoloside gave

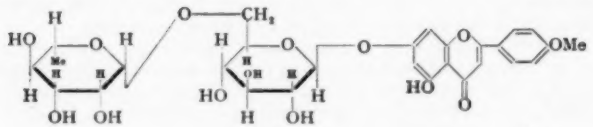
a strong ferric chloride reaction, showing that the 5-hydroxyl group was free, so that the sugars must be present as a disaccharide residue attached to the oxygen atom in position 7. This was confirmed by an examination of the completely methylated buddleoflavonoloside.

Buddleoflavonoloside was treated with methyl sulphate and aqueous sodium hydroxide, giving a hepta-*O*-methyl derivative which, on acid hydrolysis, gave 7-hydroxy-5 : 4′-dimethoxyflavone (acacetin 5-methyl ether) (VI) and a mixture of methylated sugars. Acacetin 5-methyl ether has not previously been obtained in a state of purity; it was characterised as the acetate. The mixture of methylated sugars was separated by partition chromatography (Hough, Jones, and Wadman, *loc. cit.*), giving mainly 2 : 3 : 4-trimethyl L-rhamnose (IV), and 2 : 3 : 4-trimethyl D-glucose (V), which were both characterised as their crystalline anilides.


(IV.)


(V.)


(VI.)


(VII.)

It follows that the disaccharide residue is derived from 6-(L-rhamnopyranosyl)-D-glucopyranose. The disaccharide rutinose is 6-(β-L-rhamnopyranosyl)-D-glucose, so it was considered probable that buddleoflavonoloside was 7-rutinosylacacetin. Previously the glycoside, linarin, isolated from the flowers of toad flax, *Linaria vulgaris* L., had been identified as 7-rutinosylacacetin (Merz and Wu, *Arch. Pharm.*, 1936, **274**, 126; Zemplén and Bognár, *Ber.*, 1941, **74**, 1818), and comparison of the physical properties of natural and synthetic linarin with those of buddleoflavonoloside given in Table II shows that buddleoflavonoloside and linarin are undoubtedly identical, though direct comparison of specimens has not been possible. The only apparent

TABLE II.

Compound	M. p.	$[\alpha]_D$ in acetic acid.	$[\alpha]_D$ in pyridine.
Buddleoflavonoloside	262—263° [a]; 274—276° [b] *	−98·6° [a]; −97·35° [b]	−89·6° [a]; −101·7° [b]
Natural linarin	265° [c]	−100·1° [c]	
Synthetic linarin	263—264° [d]	−100° [d]	−87·3° [d]; −88·5° [d]
Hepta-acetyl derivative of		in benzene.	
Buddleoflavonoloside	126—134° [a]	−70·3° [a]	—
Natural linarin	123—125° [c]	−70·8° [c]	—
Synthetic linarin	120—126° [d]	−71·1° [d]	—

[a] This paper. [b] Yü (1933). [c] Merz and Wu (1936). [d] Zemplén and Bognár (1941).
* Maquenne block.

difference between the buddleoflavonoloside isolated in this work, that isolated by Yü, and linarin, lies in their degree of hydration. Our analytical figures agree more closely with those required for a sesquihydrate than for a monohydrate, but the compound does not lose water at 184°; Yü does not record the presence of water of crystallisation; Merz and Wu state that linarin is a monohydrate which does not lose its water of crystallisation at 100°, whereas Zemplén and Bognár describe synthetic linarin as a monohydrate which is dehydrated at 138°.

The synthesis of linarin by Zemplén and Bognár (*loc. cit.*) from hepta-acetyl α-rutinosyl bromide (α-acetobromorutinose) and acacetin, followed by hydrolysis of the intermediate hepta-acetyl derivative, showed the β-configuration of the glycosidic linkage between the rutinose and the acacetin residues. Acetylation of buddleoflavonoloside gave a hepta-acetyl derivative which was identical with hepta-acetyl linarin (see Table II). Both buddleoflavonoloside and linarin are, therefore, represented by the formula (VII).

In view of these findings we propose that the names buddleoflavonoloside and buddleoflavonol should be no longer used, and should be replaced by linarin and acacetin respectively.

Experimental.

M. p.s are uncorrected. Analyses are by Mr. W. M. Eno, Bristol, and Drs. Weiler and Strauss, Oxford.

Isolation of Buddleoflavonoloside.—(*a*) Various parts of the shrub, *Buddleia variabilis*, were extracted and a typical experiment is given. The method first used is based upon that described by Yü (*loc. cit.*). Freshly collected leaves (300 g.) were well chopped and heated under reflux with ethanol (2·4 l.) and water (600 c.c.) for 2·5 hours. After filtration, most of the ethanol was removed by distillation under diminished pressure, and chlorophyll was removed from the aqueous residue by filtration and extraction with ether (2 × 1 l.). After being kept in a refrigerator overnight, the micro-crystalline precipitate (1·5 g., 0·5%), m. p. 260—262° (decomp.), was collected. Five crystallisations from ethanol (*ca.* 350 c.c.)–water (*ca.* 350 c.c.) gave buddleoflavonoloside (360 mg.) as cream-coloured microscopic needles, m. p. 262—263° (dependent upon rate of heating), $[\alpha]_D^{18}$ −98·6° (*c*, 0·28 in acetic acid), $[\alpha]_D^{18}$ −89·6° (*c*, 0·31 in pyridine) (Found, in material dried at 80°: C, 54·4; H, 5·7; OMe, 5·8. In material dried at 138°: C, 54·5; H, 5·7; OMe, 6·2. In material dried at 184°: C, 54·2; H, 6·0. Calc. for $C_{16}H_{32}O_{14}.H_2O$: C, 55·0; H, 5·6; OMe, 5·1%. Calc. for $C_{16}H_{32}O_{14}.1\frac{1}{2}H_2O$: C, 54·3; H, 5·65; OMe, 5·0%). An ethanol solution of buddleoflavonoloside gives a strong greenish-brown ferric chloride reaction. Similar extractions of freshly collected buds (300 g.) gave the same glycoside (average yield, 5·8 g., 1·9%) and from the freshly collected flowers (300 g.) the average yield was 5·9 g. No advantage was gained by drying these plant materials before extraction.

(*b*) The following milder method gave a purer final product. Freshly picked flowers (2 kg.) and acetone (11·5 l.) were left at room temperature for 24 hours, then filtered, and the filtrate was concentrated under diminished pressure. The aqueous residue was left in a refrigerator overnight and the brown solid collected by centrifuging. After very thorough washing with ethanol and then ether, the glycoside was obtained as cream-coloured, microcrystalline needles (9·53 g., 0·5%), m. p. 266—267° (decomp.).

Hepta-acetyl Buddleoflavonoloside.—Buddleoflavonoloside (0·3 g.), anhydrous pyridine (4 c.c.) and acetic anhydride (4 c.c.) were heated at 85—95° for 3 hours, cooled, and poured into water. The precipitate was collected, washed, dried (yield, 0·43 g.), and recrystallised from 50% aqueous ethanol, giving *hepta-acetyl buddleoflavonoloside* (0·25 g.) as colourless, crystalline aggregates, m. p. 126—134° (unaltered by further recrystallisation), $[\alpha]_D^{18}$ −58·7° (*c*, 0·56 in pyridine), $[\alpha]_D^{18}$ −70·3° (*c*, 0·27 in benzene) [Found, in material dried over phosphoric anhydride at 80° under diminished pressure: C, 56·6; H, 5·6; OMe, 3·7; Ac, 34·5. $C_{27}H_{23}O_6(OMe)(OAc)_7$ requires C, 56·9; H, 5·2; OMe, 3·5; Ac, 34·0%].

Deacetylation of Hepta-acetyl Buddleoflavonoloside.—After a solution of hepta-acetyl buddleoflavonoloside (100 mg.) had been kept in 0·1N-methanolic sodium methoxide (25 c.c.) at 0° for 24 hours, it was neutralised with dilute hydrochloric acid and the precipitated solid collected and dried (53 mg., 78%), m. p. 244—248° (decomp.). Recrystallisation from ethanol–water as before gave buddleoflavonoloside, m. p. and mixed m. p. 270° (decomp.) (Found: C, 54·2; H, 5·9%).

Hydrolysis of Buddleoflavonoloside. Isolation of 5:7-Dihydroxy-4′-methoxyflavone (Acacetin) and Identification of L-*Rhamnose and* D-*Glucose.*—Buddleoflavonoloside (3 g.) and 3% sulphuric acid (1 l.) were heated under reflux for 18 hours and left overnight. The crystalline precipitate (1·45 g., 100%), m. p. 263°, was collected and recrystallised from ethanol, giving the aglycone, 5:7-dihydroxy-4′-methoxyflavone (acacetin), as yellow needles, m. p. 263° (Found: C, 67·3; H, 4·3; OMe, 10·8. Calc. for $C_{15}H_9O_4{\cdot}OMe$: C, 67·6; H, 4·2; OMe, 10·9%). It showed no depression of m. p. when mixed with synthetic acacetin prepared as described by Robinson and Venkataraman (*J.*, 1926, 2348), who give m. p. 261°. It gave a reddish-brown ferric chloride reaction in ethanol. The diacetyl derivative, prepared by boiling the aglycone (1·0 g.) under reflux for 1 hour with anhydrous sodium acetate (3 g.) and acetic anhydride (20 c.c.) and then pouring the mixture into water (yield 1·15 g.; m. p. 203°), had m. p. and mixed m. p. with an authentic specimen of diacetyl acacetin, 204°, after crystallisation (needles) from benzene (50 c.c.) (Found: C, 65·1; H, 4·8; OMe, 8·4. Calc. for $C_{19}H_{16}O_6{\cdot}OMe$: C, 65·2; H, 4·4; OMe, 8·4%) (Robinson and Venkataraman, *loc. cit.*, give m. p. 203°).

Excess of barium carbonate was added to the acid filtrate and, after being shaken, the neutral solution was filtered and then concentrated under diminished pressure, and traces of inorganic material were removed by addition of charcoal and filtration. Complete evaporation under diminished pressure gave a syrupy mixture *M* of sugars (1·45 g.; 87% calculated on the formula $C_{18}H_{11}O_6{\cdot}C_{12}H_{21}O_9,1{\cdot}5H_2O$). A very small portion of this material was separated on a paper chromatogram (Partridge and Westall, *Biochem. J.*, 1948, **42**, 238; Flood, Hirst, and Jones, *J.*, 1948, 1679), and the sugars were located by spraying with aniline phthalate (Partridge, *Nature*, 1949, **164**, 443; Hough, Jones, and Wadman, *J.*, 1950, 1702). A mixture of D-glucose and L-rhamnose, run on the same paper, gave a precisely similar chromatogram.

Isolation of L-*Rhamnose and* D-*Glucose from Hydrolysate of Buddleoflavonoloside.*—The mixture of sugars *M* (above) was separated (see Hough, Jones, and Wadman, *J.*, 1949, 2511) on a column of powdered hydrocellulose (65 × 3·5 cm.). After washing of the column with ethanol–water (1 : 1), the sugar mixture was dissolved in the minimum quantity of water, placed on the top of the column, and when it had soaked into the hydrocellulose the column was developed with a mixture of *n*-butanol saturated with water (9 parts) and ethanol (1 part). The eluate was collected in about 5-c.c. portions, by means of an automatic receiver changer (Hough, Jones, and Wadman, *loc. cit.*). The contents of each tenth receiver were evaporated and the residue examined on a paper chromatogram using Whatman No. 1 paper and, as the mobile phase the upper layer of the mixture, *n*-butanol (50 parts), water (40 parts), and ethanol (10 parts). Tubes 90—150 contained sugar *A* (R_G 0·30), and tubes 240—360 sugar *B* (R_G 0·09).

The combined contents of tubes 90—150 were evaporated under diminished pressure, and the syrup

(sugar *A*) (583 mg., 70%, calc. on one molecule of rhamnose per glycoside molecule) was crystallised by warming it with acetone (10 c.c.)–water (0·75 c.c.), and after several days the large, colourless rhombs of L-rhamnose monohydrate (441 mg.) were collected. These had m. p. and mixed m. p. with an authentic specimen, 100°, and $[\alpha]_D^{19}$ +8·1° (*c*, 1·08 in water) (Walton, *J. Amer. Chem. Soc.*, 1921, **43**, 127, gives for L-rhamnose hydrate, $[\alpha]_D^{20}$ +8·5°), and gave an *X*-ray powder photograph identical with that given by L-rhamnose hydrate (*X*-ray photographs kindly taken by Dr. T. H. Bevan). It was further characterised as L-rhamnose benzoylhydrazone, m. p. and mixed m. p. with an authentic specimen, 188° (decomp.; m. p. dependent upon rate of heating) (cf. Hirst, Jones, and Woods, *J.*, 1947, 1048, who record m. p. 180°, and Hirst, Hough, and Jones, *J.*, 1949, 3148, who give m. p. 183°).

The combined contents of tubes 240—360 yielded a syrup (sugar *B*) (637 mg., 70% calc. on one molecule of glucose per glycoside molecule) which was crystallised from water (1·5 c.c.) and acetone (10 c.c.). This D-glucose, after being dried over phosphoric anhydride under diminished pressure at 56°, had m. p. and mixed m. p. 146°, $[\alpha]_D^{19}$ (after 24 hours) +50·8° (*c*, 0·63 in water) $[\alpha]_D$ (equilibrium value) for D-glucose +52·8°. This D-glucose was further characterised as the β-penta-acetate, m. p. and mixed m. p. 130°.

5 : 7 : 4′-*Trimethoxyflavone*.—Methyl sulphate (3 c.c.) in acetone (20 c.c.) and 30% aqueous sodium hydroxide (13 c.c.) were added simultaneously to a vigorously stirred solution of the aglycone (200 mg.) in 30% aqueous sodium hydroxide (7 c.c.) at 40—50°. After 0·5 hour water was added and the light brown solid (179 mg., 81%) was collected and crystallised from ethanol (5 c.c.), giving 5 : 7 : 4′-trimethoxyflavone as colourless needles, m. p. 156°. Czajkowski, Kostanecki, and Tambor (*Ber.*, 1900, **33**, 1991) give m. p. 156° for trimethylapigenin.

5 : 7 : 4′-*Trihydroxyflavone* (*Apigenin*).—The aglycone (300 mg.) was heated under reflux with glacial acetic acid (15 c.c.) and hydrobromic acid (15 c.c.; *d* 1·5) for 8 hours, then poured into water, and the crystals (266 mg., 93%), m. p. 346—348°, were collected. This 5 : 7 : 4′-trihydroxyflavone (150 mg.) was characterised by heating it under reflux with acetic anhydride (4·5 c.c.) and fused sodium acetate (700 mg.), giving 5 : 7 : 4′-triacetoxyflavone (203 mg., 97%) as cream-coloured needles, m. p. 182°, from ethanol (16 c.c.)–water (6 c.c.). Czajkowski, Kostanecki, and Tambor (*loc. cit.*) give m. p. 347° for apigenin, and m. p. 181—182° for triacetylapigenin.

Methylation of Buddleoflavonoloside and Hydrolysis of the Product. Isolation of 7-*Hydroxy*-5 : 4′-*dimethoxyflavone* (VI).—Methyl sulphate (60 c.c.) in acetone (180 c.c.), and 30% aqueous sodium hydroxide (180 c.c.) were added dropwise and simultaneously in five portions at two-hourly intervals to a stirred solution of buddleoflavonoloside (6 g.) in 30% sodium hydroxide (120 c.c.) at room temperature. Two hours after the last additions, the mixture was accurately neutralised with dilute hydrochloric acid, and the acetone removed under diminished pressure. The residue was extracted with chloroform (3 × 300 c.c.), and the extracts were washed with water, dried ($MgSO_4$), and evaporated, leaving crude hepta-*O*-methylbuddleoflavonoloside as a light brown product (5·7 g.), m. p. *ca.* 114°, which could not be crystallised [Found: C, 61·4; H, 7·1; OMe, 32·2. Calc. for $C_{27}H_{32}O_4(OMe)_8$: C, 60·9; H, 6·8; OMe, 35·9%]. This was then dissolved in glacial acetic acid (125 c.c.), 5% hydrochloric acid (250 c.c.) added, and the mixture heated on a steam-bath for 5 hours. After being cooled, the yellow, crystalline precipitate was collected, washed, and dried (2·12 g., 86%), m. p. 260—264° (decomp.); it gave no ferric chloride reaction. Crystallisation from ethanol (500 c.c.) (charcoal) gave 7-hydroxy-5 : 4′-dimethoxyflavone as yellow, rectangular prisms (970 mg.), m. p. 298° (decomp.) [Found: C, 68·4; H, 4·6; OMe, 20·1. $C_{15}H_8O_3(OMe)_2$ requires C, 68·4; H, 4·7; OMe, 20·8%]. Concentration of the ethanolic mother-liquors gave a second fraction (500 mg.), m. p. 294° (decomp.). This substance has not previously been obtained pure. Zemplén and Bognár (*Ber.*, 1941, **74**, 1820) give m. p. 268—268·5° for acacetin 5-methyl ether, and Narasimhachari and Seshadri (*Proc. Indian Acad. Sci.*, 1949, **30** [A], 158) give m. p. 265—267°. Vongerichten (*Ber.*, 1900, **33**, 2909) records m. p. 264°, but it seems probable that his material was acacetin (see below).

This 7-hydroxy-5 : 4′-dimethoxyflavone (200 mg.) was heated at 100° for 1 hour with acetic anhydride (8 c.c.) and fused sodium acetate (300 mg.). The solid (235 mg., 98%), m. p. 152°, obtained on pouring the mixture into ice–water (80 g.), was collected, and crystallised from aqueous ethanol and then from aqueous acetic acid, giving 7-*acetoxy*-5 : 4′-*dimethoxyflavone* as colourless needles, m. p. 152° [Found: C, 66·6; H, 5·1; OMe, 17·7. $C_{16}H_{10}O_4(OMe)_2$ requires C, 67·1; H, 4·7; OMe, 18·2%]. According to Vongerichten (*loc. cit.*) this compound has m. p. 204°, but his material was probably diacetylacacetin, which we find has m. p. 204°.

Isolation of 2 : 3 : 4-*Trimethyl* L-*Rhamnose* (IV) *and* 2 : 3 : 4-*Trimethyl* D-*Glucose* (V).—After separation of the 7-hydroxy-5 : 4′-dimethoxyflavone from the acid hydrolysate (above), the filtrate was treated with excess of saturated, aqueous lead acetate, and filtered from lead chloride, hydrogen sulphide passed in, and the filtrate concentrated to a small volume under diminished pressure. Water was then added and removed several times under diminished pressure, to remove most of the acetic acid, and the solution was finally treated with Amberlite resin IR4B until the pH was 7, after which the solution was concentrated under diminished pressure, giving a syrup. This product was separated on a column of hydrocellulose as previously described for the sugar mixture *M* (above). The solvent mixture used for development was *n*-butanol (30 parts) and light petroleum (b. p. 80—100°; 70 parts), and the contents of every tenth tube were concentrated and examined on a paper chromatogram, using as the developing solvent the upper layer of a mixture of *n*-butanol (50 parts), water (40 parts), and ethanol (10 parts). The sugar spots were located by spraying the dried papers with 1% solution of aniline phthalate in *n*-butanol and gently warming.

Tubes 41—80 contained material which gave a greyish spot (R_G 1·01), tubes 91—130 contained material which gave a red spot (R_G 1·00), tubes 131—210 contained at least three substances which gave a red spot (R_G 1·00), a grey spot (R_G 0·86), and a reddish-brown spot (R_G 0·85), tubes 211—370 contained material which gave a reddish-brown spot (R_G 0·85).

The contents of tubes 41—80 were combined and the solvent was removed under diminished pressure, giving a syrup (723 mg., 55% calc. on one trimethyl rhamnose residue per heptamethyl buddleoflavonoloside molecule). This syrup could not be crystallised, but its specific rotation, $[\alpha]_D^{16}$ +22° (*c*, 3·5 in water), and its rate of movement on the paper chromatogram indicated that it was 2 : 3 : 4-trimethyl rhamnose. Hirst and Macbeth (*J.*, 1926, 25) give $[\alpha]_D$ +24·9° for 2 : 3 : 4-trimethyl rhamnose. It was characterised as its anilide (F. Smith, *J.*, 1940, 1046) which, after several recrystallisations from light petroleum (b. p. 80—100°), was obtained as needles, m. p. 119°. A mixed m. p. with an authentic specimen, m. p. 122°, kindly supplied by Dr. J. K. N. Jones, was 120°. Smith (*loc. cit.*) gives m. p. 111° for 2 : 3 : 4-trimethyl L-rhamnose anilide.

Similarly, tubes 91—130 gave a residue (73 mg.) which, from its rate of movement and direct comparison on a paper chromatogram, was 2 : 3 : 4 : 6-tetramethyl glucose. It was not further investigated. Tubes 131—210 gave a very small amount of material which, from its behaviour on a paper chromatogram, was not homogeneous. This fraction contained at least three sugars, 2 : 3 : 4 : 6-tetramethyl glucose (R_G 1·00), a dimethyl rhamnose (R_G 0·86), and 2 : 3 : 4-trimethyl glucose (R_G 0·85). This fraction was not further investigated.

The contents of tubes 211—370 were combined and gave a non-crystalline syrup (1·014 g., 71% calc. on one trimethyl glucose residue per heptamethylbuddleoflavonoloside molecule), $[\alpha]_D^{18}$ +67·3° (equilibrium value) (*c*, 5·3 in water). For 2 : 3 : 4-trimethyl glucose, Hess and Gramberg (*Ber.*, 1939, **72**, 1905) give $[\alpha]_D^{20}$ +62·4° in water, and Irvine and Oldham (*J.*, 1921, **119**, 1756) give $[\alpha]_D^{20}$ +66·8° (equilibrium value; *c*, 4·086 in water). This syrup was compared on the same paper chromatogram with authentic specimens of 2 : 3 : 4- and 2 : 3 : 6-trimethyl D-glucose. Its rate of movement was identical with that of 2 : 3 : 4-trimethyl D-glucose. This identity was confirmed by its characterisation as 2 : 3 : 4-trimethyl D-glucose anilide, white needles, m. p. 144°, from light petroleum (b. p. 80—100°). Peat, Schlüchterer, and Stacey (*J.*, 1939, 584) give m. p. 145—146° for 2 : 3 : 4-trimethyl D-glucose anilide.

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149. *Tropolones. Part II. The Synthesis of α-, β-, and γ-Thujaplicins.*

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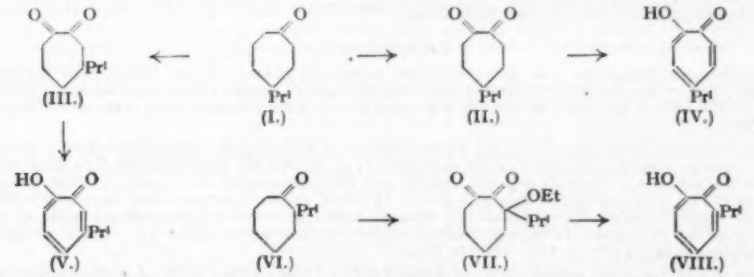
By extension of the methods described in Part I (*J.*, 1951, 503) to 2- and 4-*iso*propyl*cyclo*heptanones the naturally occurring tropolones, α- β-, and γ-thujaplicin, have been synthesised.

THE first naturally occurring compounds to be conclusively characterised as monocyclic tropolones were the α- β-, and γ-thujaplicins isolated from the heart-wood of Swedish and American Western red cedar (*Thuja plicata* D. Don). The constitutions of these substances were rigidly established as α-, β-, and γ-*iso*propyltropolones (VIII, V, and IV) respectively by the degradative work of Erdtman, Gripenberg, and Anderson (*Acta Chem. Scand.*, 1948, **2**, 625, 639, 644; *Nature*, 1948, **161**, 719; cf. also Aulin-Erdtman, *Acta Chem. Scand.*, 1950, **4**, 1031).



The antibiotic properties of these compounds, which evidently confer on the heart-wood its resistance to decay, have aroused interest (*idem, ibid.*; Southam, *Proc. Soc. expt. Biol., N.Y.*, 1946, **40**, 4409; Baillie, Freeman, Cook, and Somerville, *Nature*, 1950, **166**, 65). Erdtman has suggested that the occurrence of the thujaplicins might be of use botanically as a taxonomic criterion.

The successful conversion of *cyclo*heptanone into tropolone suggested extension of the method to the synthesis of the thujaplicins, by use of appropriate homologues of *cyclo*heptanone. One of these homologues, 4-*iso*propyl*cyclo*heptanone (I), was readily obtained by diazomethane ring expansion of 4-*iso*propyl*cyclo*hexanone. From the product of this reaction there were obtained roughly equal amounts of two isomeric semicarbazones differing widely in solubility and melting point; separate regeneration from the derivatives gave two samples of ketone, each of which gave only the semicarbazone from which it had been prepared. The thiosemicarbazones of the two samples were also different. On the other hand, the 2 : 4-dinitrophenylhydrazones and the bis-*p*-nitrobenzylidene compounds derived from the two samples were identical. The infra-red absorption spectra of the two ketones were kindly determined by Dr. F. Sondheimer at Harvard University who reported that the curves were almost identica and gave the following band assignments: An intense C=O absorption occurs at 1694 cm.$^{-1}$ with an overtone at 3390 cm.$^{-1}$; the situation of the former band at a frequency rather lower than that exhibited by other examples of saturated ketones (*ca.* 1725—1710 cm.$^{-1}$) may be due to a steric property of the seven-membered ring. The expected methylene frequency occurs at 2874 cm.$^{-1}$, and a doublet appearing at 1387 and 1370 cm.$^{-1}$ is probably due to the C–Me grouping which is known in other compounds to give rise to absorption at *ca.* 1390—1370 cm.$^{-1}$.

Geometrical isomerism about the C=N bond seems to us the most probable interpretation of the formation of isomeric semicarbazones although this does not satisfactorily explain the exclusive formation of each from its parent ketone. Similar isomeric semicarbazones were obtained from 4-methyl*cyclo*heptanone by Qudrat-I-Khuda and Ghosh (*J. Indian Chem. Soc.*, 1940, **17**, 19) who regarded them as derived from stereoisomeric forms of the parent ketones. However, it seems highly improbable that such conformations of the *cyclo*heptane ring (corresponding to the boat and chair forms of *cyclo*hexane) could exist as discrete chemical entities.

Selenium dioxide oxidation of the ketone (I) gave the expected mixture of two α-diketones (II) and (III). These were not separated, but were brominated together to give, after sodium hydroxide treatment, a mixture of sodium bromo-β- and -γ-thujaplicins. Hydrogenolysis of the latter pair led to a mixture of β- and γ-thujaplicins (V and IV) which were separated by fractional crystallisation from light petroleum.

A convenient method of preparing 2-*iso*propyl*cyclo*heptanone (VI) was found in the ring expansion of *cyclo*hexanone with diazo*iso*butane (cf. Adamson and Kenner, *J.*, 1939, 181). Selenium dioxide oxidation of (VI) in ethanolic solution brought about attack on both positions α to the carbonyl group, with formation of 3-ethoxy-3-*iso*propyl*cyclo*heptane-1 : 2-dione (VII). Such dual oxidations have been noted before, especially with compounds where a tertiary carbon atom is vicinal to the initial carbonyl group (Cauquil *et al.*, *Compt. rend.*, 1938, **208**, 1156; 1936, **202**, 326). Treatment of (VII) with bromine followed by sodium hydroxide gave sodium bromo-α-thujaplicin (presumably the ethoxyl group is replaced by bromine by virtue of its ready metathesis with the hydrogen bromide formed in the reaction). The usual hydrogenolysis procedure then yielded α-thujaplicin (VIII).

The synthetic thujaplicins did not depress the melting points of the corresponding naturally occurring compounds and gave the same tropolone reactions (green colour with ferric chloride and chloroform-soluble copper salt formation).

Experimental.

4-*iso*Propyl*cyclo*hexanone was prepared from *p-iso*propylphenol (Cook, Philip, and Somerville, *J.*, 1948, 164) by the method of Frank, Berry, and Shotwell (*J. Amer. Chem. Soc.*, 1949, **71**, 3891); it had b. p. 97—99°/15 mm. (lit., 90—91°/13 mm.) and gave a semicarbazone, m. p. 187—188° (lit., m. p. 187—188°).

4-iso*Propyl*cyclo*heptanone* (I).—To a stirred mixture of 4-*iso*propyl*cyclo*hexanone (45 g.), methanol (50 c.c.), and powdered anhydrous sodium carbonate (1 g.) was added *N*-nitrosomethylurethane (1 c.c.). After a few seconds a vigorous reaction ensued and the temperature rose sharply. Nitrosomethylurethane (78 g.) was then added dropwise during 1½ hours, the temperature being kept at 20—25° by ice-water cooling. After the addition the mixture was stirred for 1 hour and set aside at room temperature for 16 hours. Filtration, removal of solvent, and fractionation gave crude 4-*iso*propyl*cyclo*heptanone (34·5 g.), b. p. 110—114°/18 mm.

A solution of the crude ketone (52 g.) in ethanol (50 c.c.) was warmed to 50° and treated with warm ethanolic semicarbazide acetate solution [from semicarbazide hydrochloride (82 g.), potassium acetate (120 g.), and ethanol (400 c.c.)]. The crop of crystals which separated on cooling was filtered off and crystallised from aqueous ethanol; *semicarbazone*-A (33 g.) formed plates, m. p. 180—182° (strongly depressed on admixture with the semicarbazone of 4-*iso*propyl*cyclo*hexanone) (Found: C, 63·0; H, 9·7; N, 19·5. $C_{11}H_{21}ON_3$ requires C, 62·6; H, 9·95; N, 19·9%). When the mother-liquors from this compound were diluted with water a further quantity of solid separated. Repeated crystallisation

from aqueous ethanol gave the isomeric *semicarbazone*-B (24 g.) as tiny plates, m. p. 135—137° (Found: C, 62·8; H, 10·4; N, 19·7%). A mixture of the two semicarbazones melted indefinitely over the whole range between the m. p.s of the individual constituents.

Heating semicarbazone-*A* with strong aqueous oxalic acid in the usual manner quantitatively regenerated the parent ketone as a liquid with a pleasant odour, b. p. 115—117°/18 mm., n_D^{19} 1·4708 (Found: C, 77·6; H, 11·6. $C_{10}H_{18}O$ requires C, 77·9; H, 11·7%). Treatment of a small sample of this ketone with semicarbazide acetate furnished in good yield only semicarbazone-*A* with no detectable amount of the *B*-isomer. The *thiosemicarbazone*-A, prepared in the usual manner, crystallised from aqueous ethanol in tiny platelets, m. p. 156° (Found: C, 58·3; H, 9·5. $C_{11}H_{21}N_3S$ requires C, 58·15; H, 9·3%).

Similar regeneration from semicarbazone-*B* furnished the parent ketone, b. p. 114—117°/18 mm., n_D^{19} 1·4690 (Found: C, 77·6; H, 11·9%), which yielded only semicarbazone-*B* on appropriate treatment. The *thiosemicarbazone*-B formed plates, m. p. 174° (from aqueous ethanol) (Found: C, 58·35; H, 9·5%).

Both samples of ketone (*i.e.*, from semicarbazones-*A* and -*B*) on treatment with aqueous alcoholic 2 : 4-dinitrophenylhydrazine sulphate gave the same hydrated 2 : 4-*dinitrophenylhydrazone* crystallising from ethanol in yellow plates, m. p. 93—95° (Found: C, 47·7; H, 7·1; N, 13·6. $C_{16}H_{22}O_4N_4,4H_2O$ requires C, 47·35; H, 7·4; N, 13·8%); under reduced pressure the crystals lost water to give the anhydrous compound as a liquid which resolidified to the hydrate on being exposed to moist air. Reaction of both samples of ketone with *p*-nitrobenzaldehyde in the presence of ethanolic sodium ethoxide produced the same *bis*-p-*nitrobenzylidene* compound, crystallising in prisms, m. p. 151°, from *n*-butanol (Found: N, 7·1. $C_{24}H_{24}O_5N_2$ requires N, 6·7%).

Sodium Bromo-β- and γ-thujaplicins.—To a boiling solution of 4-*iso*propyl*cyclo*heptanone (9·1 g.) in ethanol (98%; 15 c.c.) was added dropwise during 1 hour a solution of selenium dioxide (7·2 g.) in ethanol (98%; 45 c.c.). Heating under reflux was continued for 6 hours after the final addition and the mixture was then kept at room temperature overnight. Removal of precipitated selenium and solvent followed by distillation gave a mixture of the diones (II) and (III) as a pale yellow liquid, b. p. 135—145°/18 mm. (7·2 g.).

A stirred solution of the diones (7·2 g.) in glacial acetic acid (8 c.c.) was cooled to 0° and treated dropwise during 1 hour with bromine (14·4 g.). The resulting deep-red solution was kept at room temperature overnight and then heated by steam until evolution of hydrogen bromide ceased (1½ hours). The acetic acid was removed by distillation in steam and the residue was extracted with ether. The ethereal extract was filtered from insoluble tarry material and then shaken with sodium hydroxide solution (6N.; 10 c.c.); the precipitated yellow *sodium* salts (1·2 g.) were filtered off and purified by crystallisation from water. Like the analogous sodium bromotropolone the salts contained two molecules of water of crystallisation (Found: C, 39·0; H, 4·2. $C_{10}H_{10}O_3BrNa,2H_2O$ requires C, 39·3; H, 4·6%).

β- and γ-Thujaplicins (V and IV).—The mixture of isomeric sodium salts (626 mg.) was dissolved in methanol (25 c.c.) and stirred under hydrogen with palladium–charcoal (10%; 150 mg.) until 1 mole of hydrogen had been absorbed. Removal of catalyst and solvent furnished a red oil which was extracted with boiling light petroleum (b. p. 40—60°). After being treated with charcoal the extract was evaporated to small bulk (*ca.* 10 c.c.) and cooled to −15°. The slightly sticky crystalline solid thus obtained was sublimed at 80° (bath-temp.)/10^{-3} mm. and the hard cream-coloured sublimate was crystallised from light petroleum (b. p. 40—60°). The resulting prismatic needles (120 mg.) had m. p. 79·5°, undepressed on admixture with naturally occurring γ-thujaplicin (m. p. 79°). Treatment with ethereal diazomethane yielded γ-thujaplicin methyl ether as a liquid, which readily yielded a *picrate* crystallising from ethanol in yellow needles, m. p. 148—149° (Found: C, 50·3; H, 4·6. $C_{17}H_{17}O_9N_3$ requires C, 50·1; H, 4·2%).

The petroleum mother-liquors from the above preparation were evaporated to dryness, leaving an oil which was distilled at 80° (bath-temp.)/10^{-3} mm. The distillate was dissolved in a small quantity of light petroleum (b. p. 40—60°), cooled to −15°, and seeded with a trace of β-thujaplicin. The solution deposited prisms, m. p. 46—47° (12 mg.) undepressed on admixture with natural β-thujaplicin (m. p. 47°).

Both β- and γ-thujaplicin were obtained in this way, not only from the mixture of ketones formed by ring-enlargement of 4-*iso*propyl*cyclo*hexanone, but also from each of the samples regenerated from the pure semicarbazones (A and B).

N-Nitrosoisobutylurethane.—To a stirred, cooled mixture of *iso*butylamine (40 g.), ether (200 c.c.), and water (100 c.c.), ethyl chloroformate (30 g.) was added dropwise, the reaction mixture being kept below 5°. A further portion of chloroformate (30 g.) and a cold solution of sodium hydroxide (22 g. in 30 c.c. of water) were then separately added dropwise at the same rate. Thirty minutes after the last addition the ethereal layer was separated and the aqueous layer extracted with ether. The combined ethereal extracts were dried (K_2CO_3); removal of solvent followed by distillation furnished *isobutylurethane* (67 g., 85%), b. p. 110°/30 mm., n_D^{17} 1·4290 (Found: N, 9·1. $C_7H_{15}O_2N$ requires N, 9·6%).

To a gently shaken mixture of the urethane (67 g.), ether (150 c.c.), sodium nitrite (150 g.), ice (46 g.), and water (230 c.c.) was added dropwise during 1 hour dilute ice-cold nitric acid [from concentrated acid (100 c.c.) and water (150 c.c.)], the temperature being kept below 15°. When the ethereal layer had become green it was separated, washed with water and potassium carbonate solution, and dried (K_2CO_3). Removal of the solvent under reduced pressure gave the *N*-nitroso*iso*butylurethane (80 g.) as a pink oil which was used without further purification for the next stage.

2-iso*Propyl*cyclo*heptanone* (VI).—A mixture of *cyclo*hexanone (47 g.), methanol (50 c.c.), and sodium carbonate (1 g.) was treated with *N*-nitroso*iso*butylurethane (80 g.) in a manner analogous to the cognate preparation described above. Fractionation of the product yielded 2-iso*propyl*cyclo*heptanone* (23 g.), b. p. 93—95°/18 mm., n_D^{18} 1·4555 (Found: C, 77·4; H, 11·6. $C_{10}H_{18}O$ requires C, 77·9; H, 11·7%).

The *semicarbazone* crystallised from aqueous ethanol in plates, m. p. 175—176° (Found: C, 62·5; H, 10·3; N, 19·95. $C_{11}H_{21}ON_3$ requires C, 62·6; H, 9·95; N, 19·9%).

3-*Ethoxy*-3-iso*propyl*cyclo*heptane*-1 : 2-*dione* (VII).—To a boiling solution of 2-*iso*propylcyclo-heptanone (23 g.) in ethanol (98%; 30 c.c.) was added dropwise during 2 hours a solution of selenium dioxide (18 g.) in ethanol (98%; 110 c.c.). After 6 hours' heating under reflux the mixture was set aside overnight and worked up as described above. Fractional distillation of the product gave the *ethoxy-dione* (VII) (13 g.) as a pale yellow oil, b. p. 130°/22 mm., n_D^{15} 1·4785 (Found: C, 68·3, 67·5; H, 9·2, 9·2; OEt, 20·7. $C_{13}H_{22}O_3$ requires C, 67·9; H, 9·5; OEt, 21·2%). The *mono*-2 : 4-*dinitrophenylhydrazone*, after preliminary purification by chromatography in benzene over alumina, crystallised from ethanol in orange rosettes, m. p. 118° (Found: N, 15·0. $C_{18}H_{24}O_6N_4$ requires N, 14·3%).

Sodium Bromo-α-thujaplicin.—A solution of the ethoxy-dione (VII) (10 g.) in glacial acetic acid (10 c.c.) was treated with bromine (20 g.) and worked up as described above. The *sodium bromo-α-thujaplicin* (2·1 g.) thus obtained crystallised from water in yellow nodules decomposing at 300° (Found: C, 40·6; H, 4·25. $C_{10}H_{10}O_2BrNa,1{\cdot}5H_2O$ requires C, 40·5; H, 4·4%). Heating the sesquihydrate to 150° *in vacuo* for 6 hours did not result in complete dehydration, only the monohydrate being formed (Found: C, 42·6; H, 4·1. $C_{10}H_{10}O_2BrNa,H_2O$ requires C, 42·45; H, 4·25%).

α-*Thujaplicin* (VIII).—A solution of the above sodium salt (400 mg.) in methanol (25 c.c.) was stirred under hydrogen in the presence of palladium–charcoal (10%; 100 mg.) until one mole of hydrogen had been absorbed. Removal of catalyst and solvent followed by extraction with boiling light petroleum (b. p. 40—60°) and evaporation gave an oil which distilled at 80° (bath-temp.)/10^{-3} mm. The distillate solidified to a feathery, frost-like mass on being cooled to 0°; crystallisation from a small volume of light petroleum (b. p. 40—60°) at −15° gave prisms of α-thujaplicin (78 mg.), m. p. 26—27° undepressed on admixture with an authentic specimen (m. p. 27—28·5°). The oily methyl ether gave a poor yield of the *picrate*, yellow needles, m. p. 110° (decomp.) (from ethanol) (Found: N, 10·6. $C_{17}H_{17}O_9N_3$ requires N, 10·3%). As the mother-liquors of this preparation furnished much unchanged liquid ether it is probable that only one of the two expected α-thujaplicin methyl ethers forms a picrate.

We are indebted to Professor H. Erdtman for kindly providing specimens of the naturally occurring thujaplicins. One of us (A. I. S.) gratefully acknowledges a Maintenance Award from the Department of Scientific and Industrial Research.

THE UNIVERSITY, GLASGOW, W.2. [*Received, December 4th*, 1950.]

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150. *The Reputed Arsenic Subsulphide.*

By F. R. HARRIS.

The reputed compound As_3S is shown not to exist.

BRUNCK (*Annalen*, 1905, **336**, 281) noted that an acidified arsenite solution treated with sodium hydrosulphite (dithionite) gave an amorphous brown precipitate of arsenic, the reaction also occurring, though more slowly, in neutral but not in alkaline solution.

Farmer and Firth (*J.*, 1926, 119; 1927, 2019) reported that the reaction product was arsenic subsulphide, As_3S, a compound which had been claimed to have been formed by an entirely different method by Scott (*J.*, 1900, 651). The existence of this compound appears not to have been generally accepted (cf. Mellor, "A Comprehensive Treatise on Inorganic and Theoretical Chemistry," Longmans, London, 1929, Vol. IX, p. 265).

The present author, as a result of roughly quantitative work, agree with Farmer and Firth's reports that, in their reaction under acid conditions, arsenite gives a precipitate which is richer in arsenic than does arsenate, and that the arsenic content of the precipitates tends to decrease with rising temperature and increasing hydrosulphite concentration.

Detailed investigation showed that precipitates obtained by Farmer and Firth's or by Scott's method consisted of mixtures of elementary sulphur and arsenic (and traces of sulphides of arsenic), which can be separated by thorough extraction. The results claimed by these authors are ascribed to incomplete extraction. The compound As_3S does not exist.

Experimental.—Farmer and Firth's claims. Precipitates were prepared from sodium arsenite (10 g.), sodium dithionite (50 g.), water (250 ml.), and (i) 2 ml. or (ii) 5 ml. of 36% hydrochloric acid. Precipitates (iii) and (iv) were prepared from the same quantities of reagents but with sodium arsenate in place of sodium arsenite. In all cases reaction was allowed to occur at 30°. The amount of acid used caused no visible difference in the colour of the precipitates, but arsenate gave chocolate-brown and arsenite black products. The precipitates were washed with water, then with alcohol and ether, and placed in a vacuum-desiccator.

All gave a negligible amount of ash on ignition. Fusion with sodium carbonate, nitrate, and peroxide resulted in some loss of arsenic, so wet oxidation was used, with a double evaporation with nitric acid; the residue, dissolved in water, was made up to a known volume and aliquot parts were used for determination of sulphur (as barium sulphate) and arsenic (as magnesium pyroarsenate). The

precipitates derived from arsenite dissolved in nitric acid rather violently, but those from arsenate much more quietly.

	Original ppt.		After $(NH_4)_2CO_3$ extraction.				After CS_2 extraction.			
			1st.		2nd.		1st.		2nd.	
Ppt. no.	As, %.	S, %.	As, %.	S, %.	As, %.	S, %.	As, %.	S, %.	As, %.	S, %.
i	92·8	7·2	96·3	3·7	96·8	3·2	98·7	1·2	99·4	0·5
ii	92·3	7·7	97·0	3·0	97·6	2·4	98·9	1·1	99·2	0·8
iii	80·9	19·1	89·8	11·5	89·8	10·2	97·1	2·8	99·0	0·9
iv	80·1	19·9	90·4	9·6	94·5	5·4	98·3	1·5	99·0	1·1

Further samples of the precipitates were extracted twice with (*a*) boiling ammonium carbonate solution or (*b*) carbon disulphide, the residues being analysed after each extraction, with the results shown in the table. It is clear from this that, although the composition varies according to the acidity and the salt used, there is no evidence that they are of the composition As_2S; thorough extraction with ammonium carbonate and carbon disulphide removes the impurities and leaves virtually pure arsenic.

Acidification of the ammonium carbonate extracts gave pure yellow precipitates, analyses of which, though varying slightly, agree fairly closely with those for As_2S_3. Evaporation of the carbon disulphide extracts yielded minute crystals which, on microscopical examination, appeared to be solely rhombic sulphur.

Scott's claims. Scott's preparation was repeated exactly, 200 g. of sodium arsenate, 3·5 l. of water, and 150 ml. of phosphorus trichloride being used. The precipitate was washed by decantation with water and alcohol, air-dried, and analysed. Four experiments yielded arsenic contents of 97·3, 96·4, 98·2, and 95·6%. The sulphur content was in all cases negligible. The precipitates were washed with dilute aqueous ammonia, then digested with concentrated ammonia solution and filtered. In no instance was a precipitate formed when the filtrates were kept, and saturation with hydrogen sulphide after acidification gave only minute amounts of bright yellow arsenic sulphide (As_2S_3; analysed). The black precipitates were suspended in concentrated ammonia solution which was then saturated with hydrogen sulphide and again filtered after 2 hours' digestion. The filtrates gave no precipitate on storage but yielded minute amounts of arsenic sulphide on acidification. At this stage the washed and alcohol-dried precipitates were again analysed, with the following results:

Ppt. no.	1	2	3	4
As, %	87·2	86·4	90·1	85·3
S, %	12·8	13·6	9·9	14·7

It will be seen that three of these four precipitates are very close to the composition As 87·7, S 12·3% calculated for As_2S.

The precipitates were next digested with hot ammonium carbonate solution for an hour, then with carbon disulphide in a Soxhlet apparatus, and the analyses repeated, with the following results:

Ppt. no.	1	2	3	4
As, %	88·4	87·9	90·8	88·1
S, %	11·6	12·1	9·1	11·9

After further extraction with carbon disulphide for 20 hours, the compositions were:

Ppt. no.	1	2	3	4
As, %	91·6	90·3	92·1	89·7
S, %	8·4	9·7	7·9	10·3

No further extractions were carried out, as it was apparent that very long solvent treatment would be necessary for complete removal of all the sulphur. It seems, however, that as in the case of Farmer and Firth's work, Scott's results can be attributed to insufficient solvent extraction, although the precipitates made by Scott's method are much more difficult to purify.

The filtrate from the black precipitates, when kept for a long time, continue to give precipitates of arsenic for several days, but after about the sixth day the precipitate was reddish and smelled strongly of phosphine or arsine. This is perhaps an adsorption phenomenon and is receiving further investigation.

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151. *The Chemistry of the Carbazoles.* 1 : 2 : 3 : 4-*Tetrahydro-4-ketocarbazoles.*

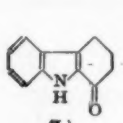
By G. R. Clemo and D. G. I. Felton.

The monophenylhydrazones of *cyclo*hexane-1 : 3-diones undergo the Fischer indole reaction to yield 1 : 2 : 3 : 4-tetrahydro-4-ketocarbazoles. The position of the keto-group has been established completely. 1 : 2 : 3 : 4 : 10 : 11-Hexahydro-2-methylcarbazole exists in two diastereoisomeric forms (α and β), both assumed to be *cis*-hexahydrocarbazoles.

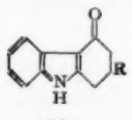
1 : 2 : 3 : 4-Tetrahydro-1-ketocarbazole (I) was long since prepared by Coffey (*Rec. Trav. chim.*, **1923**, **42**, 528) who boiled *cyclo*hexane-1 : 2-dione monophenylhydrazone (prepared by the action of benzenediazonium chloride on 2-hydroxymethylene*cyclo*hexanone) with hydrochloric acid in acetic acid. Since then a number of homologues and substituted tetrahydro-1-ketocarbazoles have been recorded (Sen and Ghosh, *J. Indian Chem. Soc.*, **1927**, **4**, 477; Lions, *J. Proc. Roy. Soc. N.S.W.*, **1933**, **66**, 516) and the action of halogens on this class of compound has been studied (Mears, Oakeshott, and Plant, *J.*, **1934**, 272). Recently interest in such compounds has re-awakened in connection with the complex reactions involved in the action of bromine followed by water on 9-benzoyltetrahydrocarbazole whereby 1 : 2 : 3 : 4-tetrahydro-1-hydroxycarbazole is formed (Plant, Robinson, and Tomlinson, *Nature*, **1950**, **165**, 928). This hydroxy-compound can be obtained by the reduction with sodium and alcohol of 1 : 2 : 3 : 4-tetrahydro-1-ketocarbazole (Moore, reported by Plant, Robinson, and Tomlinson, *loc. cit.*).

There is, however, no record of tetrahydroketocarbazoles with the keto-group in a position other than 1. In connection with another topic, we were interested in the possibility of preparing 1 : 2 : 3 : 4-tetrahydro-4-ketocarbazole (II; R = H) but, since this work is at present in abeyance, we are placing some of our observations on record.

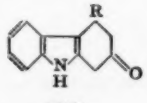
From the first, the most attractive route lay in achieving the ring-closure, under the conditions of the Fischer indole synthesis, of the monophenylhydrazone of *cyclo*hexane-1 : 3-dione, which is readily available (Merling, *Annalen*, **1894**, **278**, 39; Felton and King, *J.*, **1948**, 1371). It was found that a compound giving analyses correct for the required product could be obtained in 50—60% yield by the action of approximately 40% sulphuric acid at 100°.



(I.)



(II.)



(III.)

The compound was *N*-acetylated with difficulty by an application of the method used by Mears, Oakeshott, and Plant (*loc. cit.*), and the presence of a keto-group was shown by the formation of a deep maroon-coloured 2 : 4-dinitrophenylhydrazone.

It is clear that ring closure to a tetrahydroketocarbazole can yield (II) or (III) (R = H). The maroon colour of the dinitrophenylhydrazone suggested the conjugation of an olefinic link with the keto-group and therefore indicated structure (II; R = H), although the position was complicated by the likelihood that the intense colour was perhaps due to the polynitro-nucleus since the tetrahydroketocarbazole yielded a bright red picric acid complex. This complex is interesting in that the ratio of the two components was 1 : 1, in contrast to that obtaining with tetrahydro-1-ketocarbazole, 2 molecules of which unite with 1 molecule of the polynitro-compound (Kent, *J.*, **1935**, 976; Kent and McNeil, *J.*, **1938**, 8).

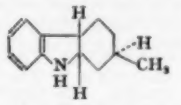
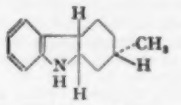
The first attempt at orientation consisted in an attempted dehydrogenation, using chloranil (Barclay and Campbell, *J.*, **1945**, 530), to yield a hydroxy-carbazole, the 1-, 2-, and 3-hydroxy-carbazoles being known. After 40 hours' reflux, a test portion still showed the presence of chloranil, and after attempted purification by chromatography, when no clear-cut fractions were obtained, the product was still an inseparable mixture which could not be crystallised. Accordingly, the properties of the tetrahydroketocarbazole were further studied.

Reduction by tin and hydrochloric acid and also electrolytically yielded *cis*-1 : 2 : 3 : 4 : 10 : 11-hexahydrocarbazole, identified by comparison with an authentic sample. While reduction of a keto-group by chemical means is well known, electrolytic reduction of a

carbonyl group is, as far as we are aware, restricted to amides. This is a further indication that (II; R = H) is the structure in question, since this contains the group $-NH-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}=O$, the vinylogue of an amide group. Electrolytic reduction of the 10 : 11-double bond of tetrahydrocarbazoles has been often observed previously.

These reduction processes, by which the carbonyl group is eliminated, offered a means of orientation if some other position in the hydrogenated portion of the molecule could be unequivocally marked relative to the carbonyl group. Thus starting from 5-methyl*cyclo*hexane-1 : 3-dione monophenylhydrazone, ring closure may yield either (II) or (III) (R = Me). Reduction will remove the carbonyl group to give 1 : 2 : 3 : 4 : 10 : 11-hexahydro-2-methylcarbazole from (II; R = Me) or 1 : 2 : 3 : 4 : 10 : 11-hexahydro-4-methylcarbazole from (III; R = Me). All four methylcarbazoles are known and the hexahydromethylcarbazoles will readily yield the dehydrogenated product (Barclay and Campbell, *loc. cit.*).

Accordingly 5-methyl*cyclo*hexane-1 : 3-dione (Vorländer and Kalkow, *Ber.*, 1897, **30**, 1802) was converted into the previously unknown monophenylhydrazone and this on treatment with *ca.* 40% sulphuric acid at 100° yielded a tetrahydroketomethylcarbazole, which gave a *N*-acetyl compound under the same conditions as above and readily formed a 2 : 4-dinitrophenylhydrazone of an identical shade of maroon, thus indicating a high probability that ring closure had occurred in the same direction as with the unmethylated compound. Reduction of the keto-compound either with tin and hydrochloric acid or electrolytically yielded a mixture of isomeric hexahydromethylcarbazoles, which gave isomeric *N*-acetyl derivatives. These were shown to be hexahydro-2-methylcarbazoles by direct comparison with the corresponding isomeric substances produced by either chemical or electrolytic reduction of 1 : 2 : 3 : 4-tetrahydro-2-methylcarbazole, when in each case an α- and a β-form were isolated. The comparison was extended to the *N*-acetyl derivatives of the hexahydro-2-methylcarbazoles in each case and completed by chloranil dehydrogenation of the hexahydrocarbazoles (α- and β-forms) to 2-methylcarbazole, identical with a sample obtained by chloranil dehydrogenation of tetrahydro-2-methylcarbazole. The orientation of the methyl group in the tetrahydromethylcarbazole and in the parent methylcarbazole had been previously established by Borsche, Witte, and Bothe (*Annalen*, 1908, **359**, 52).

(IV.)   (V.)

The yields of α- and β-forms, if losses on recrystallisation are neglected, were approximately 60% and 40% Hexahydrocarbazoles are known to give *cis*- and *trans*-isomers, but the strain in the unsubstituted *trans*-isomer is such that it is only formed to the extent of 1—2% (Gurney, Perkin, and Plant, *J.*, 1927, 2676). In the case of the unsubstituted hexahydrocarbazole, we were unable to isolate any *trans*-form when using small quantities. Consequently, we believe that the α- and β-forms are both *cis*-diastereoisomers, owing to the methyl group being *cis* or *trans* in relation to the *cis*-hydrogen atoms (cf. IV and V).

Experimental.

(All m. p.s are uncorrected.)

1 : 2 : 3 : 4-*Tetrahydro*-4-*ketocarbazole*.—*cyclo*Hexane-1 : 3-dione monophenylhydrazone (m. p. 189—192°; Merling, *loc. cit.*, gives m. p. 176—177°) (2·7 g.) was treated with sulphuric acid (10 ml.) in water (25 ml.), a dark blue-violet colour developing. The solution was warmed on the steam-bath for 1½ hours, the hot solution decanted rapidly from some tar which was produced, and then slowly diluted with water (110 ml.). A grey precipitate was obtained, which was collected, washed thoroughly with water, and dried (1·3 g.). Three recrystallisations from ethanol afforded the *carbazole* as colourless refracting rhombs, m. p. 223° (Found: C, 77·5; H, 6·2. $C_{12}H_{11}ON$ requires C, 77·8; H, 5·95%). A solution of 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid was added to an ethanolic solution of the tetrahydroketocarbazole. Slow precipitation of dark-red needles occurred and, after crystallisation from glacial acetic acid, the 2 : 4-*dinitrophenylhydrazone* formed dark maroon-coloured needles, m. p. 288° (decomp.) (Found: C, 58·9; H, 4·2. $C_{18}H_{15}O_4N_5$ requires C, 59·2; H, 4·1%). Equivalent quantities of the tetrahydroketocarbazole and picric acid were crystallised together from a little alcohol. Recrystallisation afforded the picric acid *complex* as bright red rhombs, m. p. 167° (Found: C, 52·6; H, 3·6. $C_{12}H_{11}ON,C_6H_3O_7N_3$ requires C, 52·2; H, 3·4%). The tetrahydrocarbazole (0·4 g.) in boiling acetone was treated with shaking with acetyl chloride (2 ml.) and 66% potassium hydroxide solution (3 ml.), and the product precipitated by the addition of water. It was redissolved in boiling acetone and the process repeated. The final product, crystallised from aqueous ethanol, gave the 9-*acetyl* derivative as colourless needles, m. p. 136° (Found: C, 74·2; H, 5·65. $C_{14}H_{13}O_2N$ requires C, 74·0; H, 5·7%).

Reduction.—(i) *Electrolytic reduction.* 1 : 2 : 3 : 4-Tetrahydro-4-ketocarbazole (1 g.) in 50% sulphuric acid was reduced in the cathode compartment of an electrolytic cell for 18 hours at 4—5 amps. The cathode liquor was then diluted with an equal volume of water and by addition of aqueous ammonia the base was liberated as a white precipitate. Crystallisation from aqueous ethanol afforded colourless rods, m. p. 96°, undepressed on admixture with *cis*-1 : 2 : 3 : 4 : 10 : 11-hexahydrocarbazole. The acetyl derivative was prepared by heating the base with acetic anhydride at 105—110° for ½ hour. Recrystallisation from aqueous ethanol gave needles, m. p. 97—98°, undepressed by an authentic sample of 9-acetylhexahydrocarbazole.

(ii) *Chemical reduction.* 1 : 2 : 3 : 4-Tetrahydro-4-ketocarbazole (2 g.) was added to a mixture of granulated tin (10 g.), concentrated hydrochloric acid (12 c.c.), and ethanol (12 c.c.). The mixture was refluxed for 9 hours with small additions of concentrated hydrochloric acid from time to time. The ethanol was steam-distilled from the mixture and, after cooling and basification with sodium hydroxide until the solution was strongly alkaline, the steam-distillation was continued. A white solid, practically insoluble in water was obtained, which was collected, dried, and crystallised from aqueous ethanol, yielding *cis*-1 : 2 : 3 : 4 : 10 : 11-hexahydrocarbazole, m. p. 96° undepressed by an authentic specimen of the product obtained in (i).

In neither (i) nor (ii) was any trace of isomers detected.

5-Methylcyclohexane-1 : 3-dione Monophenylhydrazone.—5-Methylcyclohexane-1 : 3-dione (1·26 g.) in dilute acetic acid was treated with phenylhydrazine (1·0 ml.) in dilute acetic acid, and the mixture warmed on the water-bath for 5 minutes. Scratching the cooled solution produced a pale yellow crystalline precipitate which on crystallisation from aqueous ethanol (charcoal) afforded the *monophenylhydrazone* as colourless rhombs, m. p. 206° (decomp.) (Found: C, 72·2; H, 7·3. $C_{13}H_{16}ON_2$ requires C, 72·2; H, 7·4%).

1 : 2 : 3 : 4-*Tetrahydro-4-keto-2-methylcarbazole.*—The above monophenylhydrazone (5 g.) was added to a mixture of sulphuric acid (20 ml.) and water (50 ml.), and the resulting brownish solution gently warmed on the steam-bath for 2 hours. Cautious dilution with water (100 ml.) produced a brownish precipitate, which after crystallisation from ethanol yielded the *tetrahydroketomethylcarbazole* as colourless needles, m. p. 259—260° (Found: C, 78·4; H, 6·8; N, 7·1. $C_{13}H_{13}ON$ requires C, 78·4; H, 6·5; N, 7·0%). The 2 : 4-*dinitrophenylhydrazone* formed very fine, iridescent, maroon needles (from glacial acetic acid), m. p. 291° (decomp.) (Found: C, 57·8; H, 4·8. $C_{19}H_{17}O_4N_5,CH_3{\cdot}CO_2H$ requires C, 57·4; H, 4·8. Found, on a sample dried at 140° in a high vacuum: C, 59·9; H, 4·3. $C_{19}H_{17}O_4N_5$ requires C, 60·2; H, 4·5%). The 9-*acetyl* derivative of the ketone, prepared as described above, formed colourless needles, m. p. 125°, from aqueous methanol (Found: C, 74·5; H, 6·3. $C_{15}H_{15}O_2N$ requires C, 74·7; 6·2%).

Reduction. 1 : 2 : 3 : 4-Tetrahydro-4-keto-2-methylcarbazole (4 g.) was added to a mixture of granulated tin (26 g.), concentrated hydrochloric acid (26 ml.), and ethanol (26 ml.). A further addition of concentrated hydrochloric acid (10 ml.) was made midway through the 9-hour period of reflux. The ethanol was removed by steam-distillation; after cooling and addition of sodium hydroxide, the passage of steam was continued, a white solid (2·2 g.) slowly distilling. Crystallisation from aqueous ethanol yielded long needles, m. p. 68—74°. These were dissolved in methanol, and water was added dropwise; addition was stopped before turbidity was reached. The solution, in the refrigerator, deposited long prisms, which were rapidly collected and recrystallised from aqueous methanol to afford *cis*-1 : 2 : 3 : 4 : 10 : 11-*hexahydro-2-methylcarbazole-α* (1·0 g.) as long colourless prisms, m. p. 81·5° (Found: C, 83·5; H, 9·4. $C_{13}H_{17}N$ requires C, 83·4; H, 9·1%). Acetylation at 105—110° for ½ hour with acetic anhydride gave the *9-acetyl* derivative, colourless small prisms, m. p. 92—93° (from aqueous ethanol) (Found: C, 78·8; H, 8·4. $C_{15}H_{19}ON$ requires C, 78·6; H, 8·3%). The mother-liquors from the crystallisation of the hexahydro-compound were concentrated and allowed to cool, colourless crystals being deposited. Recrystallised from aqueous ethanol, these yielded *cis*-1 : 2 : 3 : 4 : 10 : 11-*hexahydro-2-methylcarbazole-β* (0·7 g.) as long felted needles, m. p. 84—85° (mixed m. p. with the α-*cis*-compound, 63—70°) (Found: C, 83·3; H, 9·3%). Acetylation of the *β*-form yielded the *β*-9-*acetyl* derivative as colourless needles, m. p. 97° (mixed m. p. with the α-compound, 78—83°) (Found: C, 78·4; H, 8·1%).

Reduction of 1 : 2 : 3 : 4-*Tetrahydro-2-methylcarbazole.*—(i) 1 : 2 : 3 : 4-Tetrahydro-2-methylcarbazole (Borsche, Witte, and Bothe, *loc. cit.*) (7 g.) was refluxed for 10 hours with granulated tin (14 g.), ethanol (14 ml.), and concentrated hydrochloric acid (14 ml.). The product was isolated by steam-distillation in the usual way and was crystallised from aqueous ethanol, yielding α-*cis*-1 : 2 : 3 : 4 : 10 : 11-hexahydro-2-methylcarbazole, m. p. 81·5° undepressed on admixture with the specimen obtained above (acetyl derivative, m. p. and mixed m. p. 92—93°). On concentration of the mother-liquors, the *β*-*cis*-compound was obtained, m. p. and mixed m. p. 84—85° (acetyl derivative, m. p. 97° alone or mixed with the specimen described above).

(ii) *Electrolytic reduction.* The tetrahydrocarbazole (5 g.) was reduced electrolytically and isolated as above. Fractional crystallisation of the product from aqueous ethanol afforded both the α- (m. p. 81·5°) and the *β*-*cis*-form (m. p. 84—85°).

Dehydrogenation of cis-1 : 2 : 3 : 4 : 10 : 11-*Hexahydro-2-methylcarbazole-α.*—(i) The α-*cis*-form from the corresponding tetrahydro-keto-compound) (0·33 g.) was dissolved in xylene, chloranil (0·915 g., 2 mols.) was added, and the mixture refluxed until a test portion gave no pink colour with sodium hydroxide solution (2 hours). The solution was then cooled and filtered from the precipitated tetrachloroquinol, and the filtrate processed in the usual way. Crystallisation of the product from ethanol yielded 2-methylcarbazole as silvery glistening leaflets, m. p. 259°, alone or mixed with an authentic sample obtained from tetrahydromethylcarbazole (Barclay and Campbell, *loc. cit.*). The picrate formed orange-red prisms, m. p. and mixed m. p. 168° (Borsche *et al.*, *loc. cit.*, give m. p. 167°).

(ii) The β-*cis*-form (0·1 g.) was dehydrogenated by means of chloranil (0·3 g.) in xylene. The product on crystallisation from ethanol formed colourless leaflets of 2-methylcarbazole, m. p. 259°, undepressed by an authentic sample (picrate, m. p. and mixed m. p. 168°).

We thank the University of Durham for the award of an I.C.I. Fellowship to one of us (D. G. I. F.).

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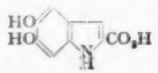
152. *Melanin and Its Precursors. Part II. Model Experiments on the Reactions between Quinones and Indoles, and Consideration of a Possible Structure for the Melanin Polymer.*

By JOHN D. BU'LOCK and JOHN HARLEY-MASON.

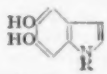
A study has been made of the reactions between indoles and quinones as models of the possible ways in which the melanin intermediate indole-5 : 6-quinone might undergo self-condensation. With certain exceptions, which are discussed, indoles unsubstituted in the 3-position condense with *o*- and *p*-benzoquinone and with 1 : 2- and 1 : 4-naphthaquinone to give intensely coloured indolylquinones. In certain cases these can react at the 2-position, if free, with a further molecule of quinone. With 3-methyl- and 2 : 3-dimethyl-indole, *p*-benzoquinone gives colourless products. The mechanism of these reactions is discussed.

From consideration of the model experiments and the behaviour of known methyl-substituted 5 : 6-dihydroxyindoles on oxidation, a polymeric structure formed by self-condensation of indole-5 : 6-quinone at the 3- and the 7-position, with cross-links involving reaction at the 2-position, is advanced for melanin.

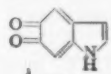
INVESTIGATIONS by Raper *et al.* (Raper, *Biochem. J.*, 1927, **21**, 89; Dulière and Raper, *ibid.*, 1930, **24**, 239) have shown that the enzymic oxidation of tyrosine leads *via* 3 : 4-dihydroxyphenylalanine and a red quinonoid oxidation product derived from it to 5 : 6-dihydroxyindole-2-carboxylic acid (I), 5 : 6-dihydroxyindole (II), and then to melanin. The two dihydroxyindole



(I.)



(II; R = H.)
(III; R = Me.)

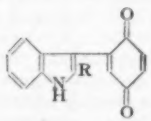


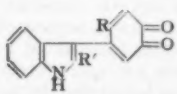
(IV.)

compounds have recently been synthesised (Beer, Clarke, Khorana, and Robertson, *J.*, 1948, 2223), and a comparison of their properties indicates that (II) rather than (I) is the actual precursor of melanin, a conclusion supported by the work of H. S. Mason (*J. Biol. Chem.*, 1948, **172**, 83).

H. S. Mason has also suggested that the formation of indole-5 : 6-quinone (IV) may be the first stage in the oxidative polymerisation of (II) to melanin. In order to throw some light on the possible ways in which (IV), regarded as a bifunctional compound, being both an indole and a quinone, might polymerise, we have studied the interaction of some simple indoles and quinones as models. Apparently, the only comparable reaction on

(V; R = Me.)
(VI; R = H.)





(VII; R = R′ = H.)
(VIII; R = Me, R′ = H.)
(IX; R = H, R′ = Me.)

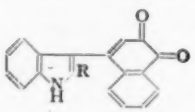
record is that between *p*-benzoquinone and 2-methylindole to give an intensely violet product, 2′-methyl-3′-indolyl-1 : 4-benzoquinone (V), obtained by boiling 2-methylindole (1 mol.) with *p*-benzoquinone (2 mols.) in ethanol (Mohlau and Redlich, *Ber.*, 1911, **44**, 3605). We confirmed this observation and found moreover that the condensation was strongly catalysed by acid, even by a little acetic acid added to the ethanol. When boiling acetic acid alone was

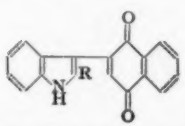
used as solvent, the reaction proceeded a stage further and a mixture of (V) and a very sparingly soluble product formed by the condensation of (V) with a second molecule of 2-methylindole, *viz.*, 2 : 5-di-(2-methyl-3-indolyl)-1 : 4-benzoquinone was obtained. Mohlau and Redlich were unable to isolate any pure product from the reaction of *p*-benzoquinone and indole ; we found, however, that the expected analogue of (V), *viz.*, 3′-indolyl-1 : 4-benzoquinone (VI), can be obtained by reaction in ethanol in the presence of hydrochloric acid. The yield was, however, poor and other ill-defined by-products were also formed. Reaction in boiling acetic acid led to the formation of a sparingly soluble red compound by condensation of two molecules of quinone with one of indole. This compound proved difficult to purify, but was regarded as 2 : 3-di-*p*-benzoquinonylindole by analogy with the corresponding naphthaquinone compound (XIV). 2 : 5- and 2 : 6-Dimethyl-1 : 4-benzoquinone failed to react with indole.

Reactions involving indoles and *o*-quinones were next examined. From indole and *o*-benzoquinone, 4-3′-indolyl-1 : 2-benzoquinone (VII) was readily obtained by reaction in aqueous ethanol at room temperature, and similarly 4-3′-indolyl-5-methyl-1 : 2-benzoquinone (VIII) from indole and 4-methyl-1 : 2-benzoquinone and 4-(2-methyl-3-indolyl)-1 : 2-benzoquinone (IX) from 2-methylindole and *o*-benzoquinone. All three compounds formed deep-violet prisms with a bronze reflex and gave deep-blue or blue-violet solutions in organic solvents. From 2-methylindole and 4-methyl-1 : 2-benzoquinone no product could be obtained, probably owing to steric hindrance (see below). It is noteworthy that the two *o*-quinones are more reactive towards indoles than is the *p*-quinone and that the reaction is complete at room temperature in 5 minutes. No product could be obtained from the attempted reaction of 4 : 5-dimethyl-1 : 2-benzoquinone with indole or 2-methylindole. This quinone was first prepared by Diepolder (*Ber.*, 1909, **42**, 2921) by oxidation of 5-amino-*o*-4-xylenol with aqueous acid dichromate : having encountered some difficulty with this reaction, we sought an alternative. *o*-4-Xylenol was oxidised with alkaline persulphate to give a low yield of 4 : 5-dimethylcatechol (cf. oxidation of *p*-cresol ; G.P. 81,289) and this on oxidation with silver oxide in ether gave an excellent yield of the quinone.

Reactions between indoles and naphthaquinones were then investigated. Herter (*J. Biol. Chem.*, 1904, **1**, 247) observed that indole reacted with solutions of sodium 1 : 2-naphthaquinone-4-sulphonate giving a deep-violet colour, but did not isolate any pure product. We have re-investigated this reaction and have isolated 4-3′-indolyl-1 : 2-naphthaquinone (X) and, from 2-methylindole, 4-(2-methyl-3-indolyl)-1 : 2-naphthaquinone (XI). The yield of the latter was much lower, probably owing to steric hindrance (see below). The same products

(X ; R = H.)
(XI ; R = Me.)





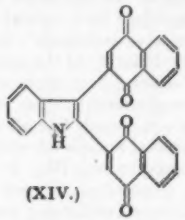
(XII ; R = Me.)
(XIII ; R = H.)

were obtained when 1 : 2-naphthaquinone was employed instead of the 4-sulphonate. 2-Methylindole and 1 : 4-naphthaquinone reacted readily in ethanol containing acetic acid to give 2-(2-methyl-3-indolyl)-1 : 4-naphthaquinone (XII) which formed almost black prisms giving deep-violet solutions in organic solvents, whereas indole and 1 : 4-naphthaquinone in acetic acid gave a mixture of two products, the more soluble giving intensely violet solutions and closely resembling (XII), and the other, very sparingly soluble, forming brilliant red needles which separated from the boiling solvent as the reaction proceeded. Analysis indicated that the first product contained one indole and one naphthaquinone residue and was thus 2-3′-indolyl-1 : 4-naphthaquinone (XIII) analogous to (XII), whereas the second product contained two naphthaquinone residues and was therefore formulated as 2 : 3-di-(1 : 4-naphthaquinon-2-yl)indole (XIV). This formulation is supported by the fact that (XIV) can be obtained by reaction of (XIII) with a further molecule of 1 : 4-naphthaquinone, and that (XII), in which the 2-position is blocked, does not react further with the naphthaquinone. Since (XIII) is presumably first formed, it was hoped that, by conducting the reaction under milder conditions, formation of (XIV) might be avoided, but under all conditions examined the mixture was invariably obtained. 2-Methyl-1 : 4-naphthaquinone failed to react with indole under the above conditions.

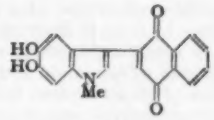
To test the effect on the reaction with quinones of substituents in the indole *Bz*-nucleus, the reaction between 2-methyl-5 : 6-methylenedioxyindole (Burton and Duffield, *J.*, 1950, 78) and *p*-benzoquinone was examined. The presence of the methylenedioxy-group did not appear

to affect materially the course of the reaction, and the expected 2′-methyl-5′ : 6′-methylenedioxy-3′-indolyl-1 : 4-benzoquinone was obtained, with properties very similar to those of (V). However, neither 5 : 6-methylenedioxyindole-2-carboxylic acid nor its ethyl ester could be induced to react with quinones at all, and it appears that the reactivity of the 3-position is completely abolished by the adjacent carboxyl group.

5 : 6-Dihydroxy-1-methylindole (III) (Harley-Mason, *J.*, 1950, 1276) was found to be oxidised to melanin-like products by all the quinones examined, except 1 : 4-naphthaquinone, with which it condensed readily in cold aqueous acetic acid solution to give 2-(5 : 6-dihydroxy-1-methyl-3-indolyl)-1 : 4-naphthaquinone (XV), which separated as deep violet needles. In



(XIV.)



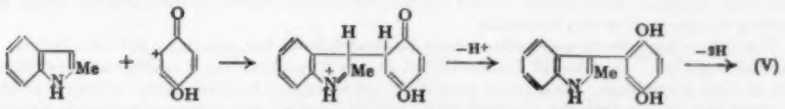
(XV.)

this case it is evident that the hydroxyl groups in the indole nucleus accelerate the reaction considerably, since 1 : 4-naphthaquinone and indole itself react much more slowly under the same conditions. With an excess of the naphthaquinone in boiling acetic acid solution, the product was 5 : 6-dihydroxy-1-methyl-2 : 3-di-(1 : 4-naphthaquinon-2-yl)indole, analogous to (XIV).

All the foregoing experiments describe reactions between quinones and indoles unsubstituted in the 3-position, and the products, except those of type (XIV), all have very similar properties, giving intensely coloured (blue or violet) solutions in ethanol, changing to green or bluish-green on the addition of alkali. To demonstrate that products of this type can only be obtained by reaction at the 3-position, an acetic acid solution of equimolecular amounts of 3-methylindole (scatole) and *p*-benzoquinone was kept at room temperature; the solution slowly became violet-red and a crystalline substance separated, of empirical formula $C_{13}H_{10}ON$; this, if doubled, indicates reaction of 2 mols. of scatole and 1 mol. of *p*-benzoquinone with the loss of 2 hydrogen atoms. A similar product was obtained (though in lower yield) from 2 : 3-dimethylindole and *p*-benzoquinone. Both products were colourless, had high melting points (250—252° and 345—348°, respectively), and were very sparingly soluble in all solvents. They were completely unaffected by aqueous alkali, indicating the probable absence of phenolic hydroxyl groups, but afforded diacetyl derivatives with boiling acetic anhydride. In these the acetyl groups were thus presumably attached to nitrogen, indicating that the molecule probably contains two dihydroindole rings, since indole is not acetylated under these conditions. These compounds were not further studied, and on the above evidence they cannot be assigned a structure, but it is quite clear that they are entirely different from the products obtained from benzoquinone and indoles unsubstituted in the 3-position.

Discussion.

(1) *Mechanism of the Reaction between Indoles and Quinones.*—Mohlau and Redlich (*loc. cit.*) interpret the reaction between 2-methylindole and *p*-benzoquinone as proceeding in two stages : (*a*) addition of the indole to the quinone with the transfer of two hydrogen atoms to give the indolylquinol (XVI); (*b*) oxidation of (XVI) to the corresponding quinone (V) by a second molecule of benzoquinone :

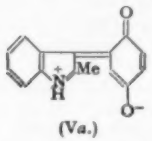


(XVI.)

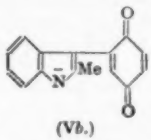
The fact that the reaction is strongly catalysed by acids indicates that the conjugate acid of the quinone is probably the reactive entity involved, so the reaction may be represented as in the scheme. Electron density in the indole nucleus is maximal in the 3-position (Longuet-

Higgins and Coulson, *Trans. Faraday Soc.*, 1947, **43**, 87), so reaction at this point with a strongly cationoid reagent is to be expected. A similar scheme would apply to the reactions of indole and 2-methylindole with *o*-quinones.

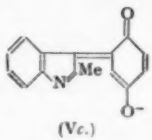
The 3-indolylquinones obtained in this way all have similar properties : They are lustrous crystalline solids, varying in colour from blue-violet to almost black. They are almost insoluble in water but soluble in organic solvents, giving intensely blue-violet solutions. The absorption spectra (Figs. 1, 2, and 3) indicate clearly that they may be regarded as vinylogues of amino-quinones, the indole-nitrogen atom being conjugated with the quinone nucleus. This conjugation is responsible for the principal absorption maximum in the 5200—6000-A. region shown by all the compounds; it results also in a lowering of the oxidation potential of the reduced form (*e.g.*, XVI) so that oxidation to the indolyl-quinone by a second molecule of the original quinone is facilitated. The conjugation implies a considerable contribution from zwitterionic mesomeric structures, such as (V*a*), requiring coplanarity of the indole and quinone nuclei. Inspection of a scale drawing of 4-2′-methyl-3′-indolyl-1 : 2-naphthaquinone shows that there will be considerable steric hindrance of such coplanarity. This is confirmed not only by the slow rate of formation and poor yield of this compound, but also by the greatly reduced intensities of its absorption bonds at 4000 and 5600 A. compared with those at 4000 and 5200 A. in the unhindered compound (X) lacking the methyl group (Fig. 3). The bands at lower wave-lengths correspond to more localised electron transitions and are not affected in this way by the coplanarity criterion. This is a particular case confirming the generalisation that the colour of these compounds is due to the type of conjugation here considered.



(V*a*.)



(V*b*.)



(V*c*.)

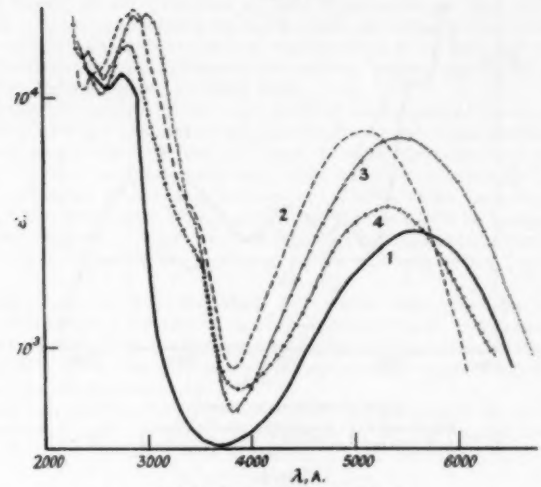
Further evidence in favour of this view is provided by the behaviour of these compounds in alkaline solution. They behave as weak acids and form ions with an intense blue or green colour. Their absorption spectra (Fig. 4) (in some cases only approximate because of the rather rapid decomposition of the solutions) all show intense long-wave-length (*ca.* 6500 A.) absorption which is ascribed to resonance between structures such as (V*b*) and (V*c*). Since the low-energy transition corresponding to the 5100-A. bond of the neutral molecule (V ⟷ V*a*) involves charge separation whilst that in the anion (V*b* ⟷ V*c*) does not, the latter transition is even more favoured and the absorption of its anion is of higher intensity. The same steric factors should be operative in the anion of (XI) as in the neutral molecule, and in fact comparison of the absorption spectra (Fig. 4) of the anions of (XI) and (X) shows that the effect is even more marked here than in the neutral molecules.

Inspection of a scale drawing of 5-methyl-4-(2-methyl-3-indolyl)-1 : 2-benzoquinone shows that the 5-methyl group overlaps the indole 4-position and the 2-methyl group, preventing coplanarity. In this case the steric effect is so large that all attempts to obtain this compound by reaction of 4-methyl-1 : 2-benzoquinone and 2-methylindole were unsuccessful, whereas the two compounds (VIII) and (IX), lacking either of the methyl groups, were readily obtained.

The failure of 2 : 5- and 2 : 6-dimethyl-1 : 4-benzoquinones, 4 : 5-dimethyl-1 : 2-benzo-quinone, and 2-methyl-1 : 4-naphthaquinone to react with indoles is also probably due to steric hindrance : Madinaveitia (*Anal. Fís. Quím.*, 1933, **31**, 750) has commented on the lower reactivity of 2-methyl-1 : 4-naphthaquinone than of 1 : 4-naphthaquinone towards nucleophilic reagents. On the other hand, the failure of 5 : 6-methylenedioxyindole-2-carboxylic acid to react with quinones is probably caused by the electromeric effect of the carboxyl group with-drawing electrons from the 3-position.

The following general conclusions may be drawn from the reactions between indoles and quinones studied : (1) Indoles unsubstituted in the 3-position react readily at this position with *o*- and *p*-quinones, undergoing oxidative condensation to give highly coloured products in which the indole and the quinone rings are conjugated and coplanar or nearly coplanar. (2) If the indole 2-position is free, reactions with a second molecule of quinone may occur at this position. (3) The reaction is catalysed by acids, the uncatalysed reaction being much slower. *o*-Quinones are more reactive than *p*-quinones. (4) Substituents in other positions (apart from carboxyl in the 2-position, which prevents reaction altogether) do not directly

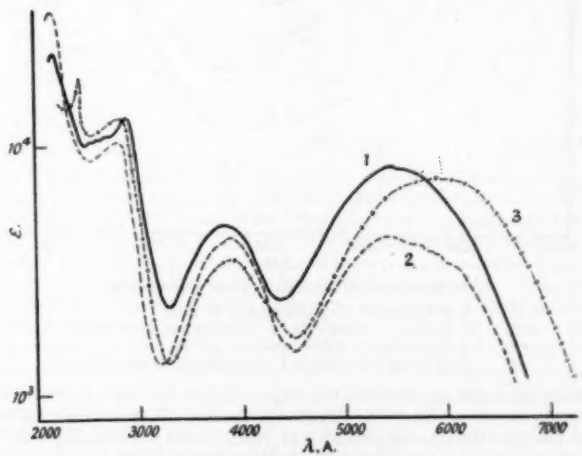
FIG. 1.



Light absorption in ethanol of :

1. 2′-*Methyl*-3′-*indolyl*-1 : 4-*benzoquinone* (V).
2. 2-3′-*Indolyl*-1 : 4-*naphthaquinone* (XIII).
3. 2-(5 : 6-*Dihydroxy*-1-*methyl*-3-*indolyl*)*naphtha*-1 : 4-*quinone* (XV).
4. 2-(2-*Methyl*-3-*indolyl*)-1 : 4-*naphthaquinone* (XII).

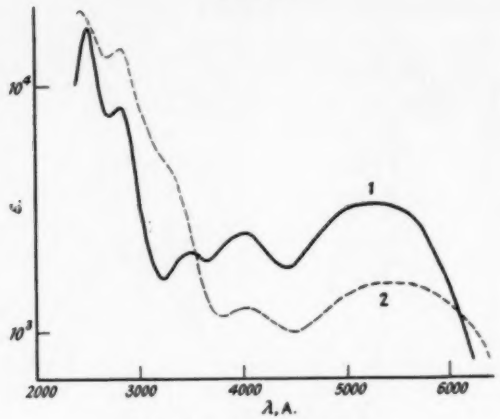
FIG. 2.



Light absorption in ethanol of :

1. 4-3′-*Indolyl*-1 : 2-*benzoquinone* (VII).
2. 5-3′-*Indolyl*-4-*methyl*-1 : 2-*benzoquinone* (VIII).
3. 4-(2-*Methyl*-3-*indolyl*)-1 : 2-*benzoquinone* (IX).

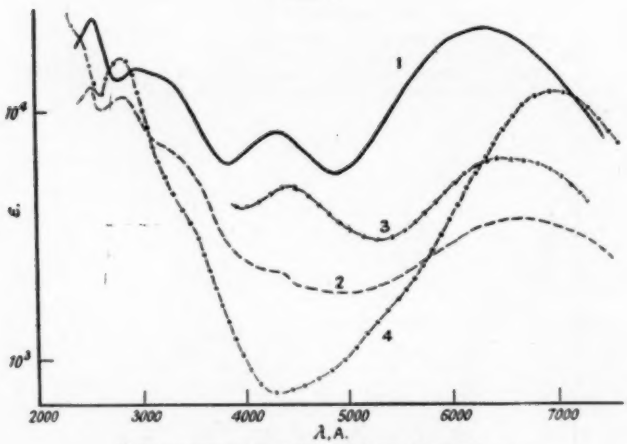
FIG. 3.



Light absorption in ethanol of :

1. 4-3′-*Indolyl*-1 : 2-*naphthaquinone* (X).
2. 4-(2-*Methyl*-3-*indolyl*)-1 : 2-*naphthaquinone* (XI).

FIG. 4.



Light absorption in alcoholic sodium hydroxide of :

1. 4-3′-*Indolyl*-1 : 2-*naphthaquinone* (X).
2. 4-(2-*Methyl*-3-*indolyl*)-1 : 2-*naphthaquinone* (XI).
3. 4-3′-*Indolyl*-1 : 2-*benzoquinone* (VII).
4. 2-(2-*Methyl*-3-*indolyl*)-1 : 4-*naphthaquinone* (XII).

affect the course of the reaction provided that steric effects are not involved : in the one case of a 5 : 6-dihydroxyindole studied, the hydroxyl groups are found to facilitate reaction. (5) Steric effects are particularly important : in cases where overlapping substituents would cause large deviations from coplanarity of the product, the reaction proceeds with difficulty or not at all. (6) When the indole 3-position is blocked, reaction follows a different course, and colourless products are formed.

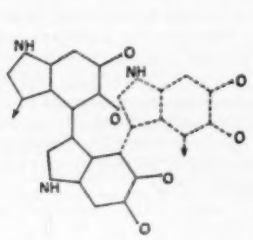
(2) *The Structure of Melanin.*—Three monomethyl-substituted 5 : 6-dihydroxyindoles have recently been synthesised, and their oxidation studied. 5 : 6-Dihydroxy-1- and -2-methylindole give " methyl-melanins " (Burton, *Chem. and Ind.*, 1947, 283) whereas the 3-methyl compound

(Beer, McGrath, Robertson, and Woodier, *J.*, 1949, 2061) does not, thus suggesting that the 3-position of 5 : 6-dihydroxyindole is directly concerned in the oxidative polymerisation to melanin. Experiments on the oxidation of (III) (Harley-Mason, *loc. cit.*) have shown that hydroxylation at position 3 is unlikely to be involved, since the product which would thus be obtained, 3 : 5 : 6-trihydroxy-1-methylindole, was synthesised by another route and found to give 5 : 6 : 5′ : 6′-tetrahydroxy-1 : 1′-dimethylindigo on further oxidation, and this is quite unlike melanin (cf. Harley-Mason, *J.*, 1948, 1244).

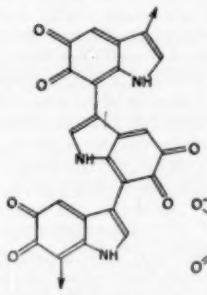
The most likely alternative is that an oxidative condensation occurs at the 3-position. Indirect evidence that this condensation may be similar to the indole–quinone reactions which we have studied, is provided by the fact that 5 : 6-dihydroxyindole-2-carboxylic acid, in contradistinction to the 2-methyl compound, does not give melanin on autoxidation (Beer *et al.*, *loc. cit.*). Further, Clemo and Duxbury (*J.*, 1950, 1795) have shown that enzymic oxidation of tyrosine ethyl ester gives a brown pigment in which the carboxyethyl residue is retained and which differs in many respects from tyrosine-melanin. These results could be accounted for by deactivation of the 3-position by the adjacent carboxyl group [cf. conclusion (4), above].

A polymerisation of indole-5 : 6-quinone (IV) could take place by repeated oxidative condensation involving the 3-position of one molecule and the 4- or 7-position of another, the condensation being analogous to the indole–quinone reactions described above. Scale diagrams (XVII) and (XVIII) show the two structures which would thus be obtained, three of the repeating units being shown in each case.

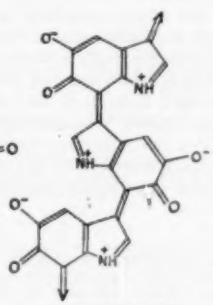
It will be seen that (XVII), the structure derived by condensation in the 4-position, cannot possibly be coplanar and therefore, by analogy with the model experiments above [cf. conclusion (5)], it is unlikely that a product of this structure could be formed at all



(XVII.)



(XVIII.)



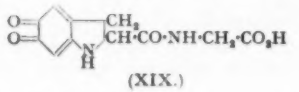
(XVIII*a*.)

easily. No such difficulty arises with (XVIII), and moreover the quinone rings are conjugated with the indole-nitrogen atoms of the neighbouring units (as in the canonical structure XVIII*a*). Extensive conjugation of this kind throughout long chains of varying length would account for the intense light-absorption over a wide range of wave-lengths which melanin displays. The extreme insolubility of melanin suggests that, although polymer chains such as (XVIII) may form " backbone units," some sort of cross-linking is probably present. This could be provided by condensation at the free 2-position with the 4- or the 7-position of another molecule, a process analogous to the formation of indolyl-2 : 3-diquinones described above. Reaction at the 2-position would occur less readily than at the 3-position, but the occurrence of a few such links would be sufficient to build up a highly irregular three-dimensional polymer.

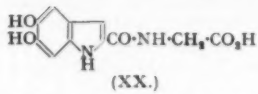
The repeating unit in (XVIII) has the empirical formula $C_8H_3O_2N$: derivation of such a structure by oxidation of tyrosine would require consumption of 5 atoms of oxygen per molecule, in good agreement with Dulière and Raper's results (*loc. cit.*). Analytical figures for tyrosine-melanin lead to empirical formulæ $C_8H_5O_3N$ (*idem*) and $C_{16}H_{10}O_5N_2$ (Burton, *loc. cit.*). The first differs from $C_8H_3O_2N$ by $1H_2O$ and the second from $2C_8H_3O_2N$ by $1H_2O$ and 2 hydrogen atoms. Two other condensed 5 : 6-dihydroxyindole derivatives (5 : 6 : 5′ : 6′-tetrahydroxy-indigo and its *NN*′-dimethyl derivative; Harley-Mason, *loc. cit.*) have been shown to retain water extremely firmly, and it is suggested that this same firm retention occurs in melanin—such retention by a cross-linked amorphous polymer is *a priori* not unlikely.

Bawn and White (quoted by Beer *et al., loc. cit.*) have found that the autoxidation of 5 : 6-dihydroxyindole shows the characteristics of an oxidative chain reaction and is susceptible to trace-metal catalysis. If the polymerisation proceeds by a radical-chain mechanism, the initiating radical is most probably not (IV) but the corresponding semiquinone formed by loss of one hydrogen atom from (II). The model indole–quinone reactions we have described are almost certainly ionic in mechanism and it is possible that a radical-mechanism polymerisation may proceed differently. None the less, we regard a cross-linked polymer based on (XVIII) as the most satisfactory structure for melanin on present evidence. A test of its validity would be provided by the investigation of the oxidation of a 5 : 6-dihydroxyindole substituted in the 7-position, which should not give a melanin, and we are engaged upon the synthesis of such a compound.

Melanins isolated from natural sources are usually conjugated with protein, and in an attempt to throw some light on the nature of this conjugation we have examined the oxidation with mushroom tyrosinase of the dipeptide tyrosylglycine. This oxidation led to a bright red solution having an absorption spectrum almost identical with that of the red quinone obtained by similar oxidation of tyrosine itself. Continued oxidation led to a brown solution, but no precipitate of melanin was obtained. When the red solution was kept under nitrogen it was slowly decolorised and an ethereal extract then exhibited a bluish-violet fluorescence in ultra-violet light and gave a green colour with ferric chloride. Evidently the oxidation of the dipeptide proceeds initially in the same manner as that of tyrosine, through the red quinone



(XIX.)



(XX.)

(XIX) to the dihydroxyindole compound (XX), and it would be expected that a tyrosyl end-group of a protein would behave similarly. Similar behaviour of a tyrosyl residue in the middle of a peptide chain is, however, very improbable, since it has been shown that *N*-formyl- and *N*-acetyl-tyrosine are not oxidised by tyrosinase (Lerner, Fitzpatrick, and Summerson, *Fed. Proc.*, 1949, **8**, 218), so the presence of an unacylated amino-group appears to be essential. In (XX) the 3-position is deactivated so that oxidative polymerisation to give a melanin does not occur, but the 7-position remains free for oxidative coupling with dihydroxyindole derived from unbound tyrosine. In this way a polymer could be build up having an end group such as (XX) in which the glycine residue was replaced by a protein chain.

Experimental.

Reaction of p-*Benzoquinone with Excess of* 2-*Methylindole.*—A solution of 2-methylindole (1·5 g.) and *p*-benzoquinone (1 g.) in acetic acid (25 c.c.) was heated under reflux for 5 hours. After cooling, the product was filtered off and recrystallized from nitrobenzene. 2 : 5-*Di*-(2-*methyl*-3-*indolyl*)-1 : 4-*benzoquinone* formed small brownish-violet plates, m. p. 294—296°, and was very sparingly soluble in all the usual solvents (Found : C, 78·4; H, 5·1; N, 7·7. $C_{24}H_{18}O_2N_2$ requires C, 78·7; H, 4·9; N, 7·6%). Light absorption in acetone : max. 4980 A.; $\varepsilon = 6620$.

Reaction of p-*Benzoquinone with Indole.*—(*a*) To a solution of indole (1 g.) and *p*-benzoquinone (2 g.) in ethanol (100 c.c.) 5 drops of concentrated hydrochloric acid were added with stirring. After 10 minutes at room temperature, the deep-violet solution was diluted with water (100 c.c.). A precipitate separated, consisting of deep violet needles admixed with greenish-yellow amorphous material. This was collected by filtration and extracted with cold aqueous 2% sodium hydroxide, which dissolved the amorphous material. The residue was recrystallized by warming it with ethanol to 50°, filtering, and cooling the filtrate to −30°. 3′-*Indolyl*-1 : 4-*benzoquinone* formed deep violet-black needles which decomposed without melting at *ca.* 140°, and gave reddish-violet solutions in ethanol, acetic acid, and benzene which decomposed very rapidly on heating (Found : C, 74·9; H, 3·7. $C_{14}H_9O_2N$ requires C, 75·2; H, 4·0%).

(*b*) A solution of indole (1·2 g.) and *p*-benzoquinone (3·5 g.) in acetic acid (50 c.c.) was heated under reflux. The solution rapidly became violet and then red, and some reddish solid soon began to separate. After 2 hours' boiling, the material was filtered off hot and twice recrystallised from nitrobenzene. It formed a dull red powder which remained unmelted below 360°, was almost insoluble in all the usual solvents, and was substantially 2 : 3-*di*-p-*benzoquinonylindole* (Found : C, 74·0; H, 3·4; N, 4·6. $C_{20}H_{11}O_4N$ requires C, 73·0; H, 3·35; N, 4·3%).

Reaction of o-Benzoquinone with Indole and 2-*Methylindole.*—Catechol (2·5 g.) was dissolved in dry ether (70 c.c.), and the solution shaken for 20 minutes with silver oxide (10 g.) and anhydrous sodium sulphate (10 g.). The solids were filtered off, and the filtrate cooled to −40°. After 10 minutes, the crystals of *o*-benzoquinone were filtered off and dissolved at once in aqueous ethanol (20 c.c.; 1 : 1). A solution of indole (0·2 g.) in aqueous ethanol (10 c.c.; 1 : 1) was added immediately. The mixture at once became deep violet and the product rapidly separated. After 3 minutes it was collected and

purified by dissolution in acetone at room temperature, filtering, and cooling the filtrate to −40°. 4-3′-*Indolyl*-1 : 2-*benzoquinone* (Found : C, 74·3; H, 4·0; N, 6·3. $C_{14}H_9O_2N$ requires C, 75·2; H, 4·0; N, 6·3%) formed small violet needles with a bronze reflex, m. p. 160° (decomp.). Light absorption in ethanol : Max., 2170, 2880, 3780, and 5390—5430 A.; ε = 24,200, 13,500, 4870, and 8140, respectively. The deep-violet solutions in ethanol and acetone decomposed very rapidly when warmed. Alcoholic sodium hydroxide gave a transient intense greenish-blue colour. Reduction with sodium dithionite afforded a colourless solution with a strong violet fluorescence.

Repetition of the above procedure using 2-methylindole in place of indole gave 4-(2-*methyl*-3-*indolyl*)-1 : 2-*benzoquinone*, m. p. 171° (decomp.) (Found : C, 76·3; H, 4·9. $C_{15}H_{11}O_2N$ requires C, 75·9; H, 4·7%). Light absorption in ethanol : Max. 2450, 2820, 3940, and 5950 A.; ε = 19,000, 12,700, 3500, and 7400, respectively. This compound was much more stable in solution than its lower homologue, and was recrystallised from boiling ethanol.

Reaction of 4-*Methyl*-1 : 2-*benzoquinone with Indole.*—(*a*) 4-Methyl-1 : 2-benzoquinone was prepared as described above, 4-methylcatechol being used in place of catechol. The quinone (0·6 g.) in aqueous ethanol (30 c.c.; 1 : 1) was added to a solution of indole (0·3 g.) in ethanol (10 c.c.). The product separated rapidly from the violet solution and was collected and recrystallised from ethanol. 4-3′-*Indolyl*-5-*methyl*-1 : 2-*benzoquinone* formed violet prisms, m. p. 158° (Found : C, 75·4; H, 4·6; N, 5·8. $C_{15}H_{11}O_2N$ requires C, 75·9; H, 4·7; N, 5·9%). Light absorption in ethanol : Max., 2180, 2810, 3880, and 5460—5510 A.; ε = 36,400, 10,530, 4500, and 4520, respectively.

(*b*) To a solution of 4-methylcatechol (1·2 g.) in water (100 c.c.), a solution of indole (1·1 g.) in ethanol (50 c.c.) was added, and to this a solution of potassium ferricyanide (13·2 g.) and sodium hydrogen carbonate (3·4 g.) in water (80 c.c.) was added slowly with stirring. The product, which separated rapidly as deep violet needles, was collected and recrystallised as above.

Reaction of Sodium 1 : 2-*Naphthaquinone*-4-*sulphonate with Indole and* 2-*Methylindole.*—The sulphonate (recrystallised; 0·5 g.) was dissolved in boiling water (30 c.c.) and added to a solution of indole (0·25 g.) in water containing a little ethanol at 100°. The product rapidly separated in crystalline form, and was collected and recrystallised from nitrobenzene. 4-3′-*Indolylnaphtha*-1 : 2-*quinone* formed purple needles, m. p. 272—275° (decomp.) (Found : C, 79·5; H, 4·7; N, 4·9. $C_{18}H_{11}O_2N$ requires C, 79·2; H, 4·1; N, 5·1%). Light absorption in ethanol : Max., 2520, 2800, 3450, 4000, and 5150 A.; ε = 17,000, 8100, 2050, 2500, and 3200, respectively. It was sparingly soluble in acetone, ethanol, and acetic acid, giving reddish-purple solutions.

When the above procedure was repeated but with 2-methylindole in place of indole, the reaction was much slower and the product separated during several hours as an amorphous purple powder. This was purified by chromatography from a chloroform solution on alumina. After elution and removal of the solvent, 4-2′-*methyl*-3′-*indolyl*-1 : 2-*naphthaquinone*, purple needles, m. p. 200—205° (decomp.), was recrystallised from nitrobenzene (Found : C, 79·2; H, 4·7; N, 5·1. $C_{19}H_{13}O_2N$ requires C, 79·4; H, 4·5; N, 4·9%). Light absorption in ethanol : Max., 2500, 2800, 4000, and 5600 A.; ε = 18,000, 14,000, 1200, and 1600, respectively.

Reaction of 1 : 4-*Naphthaquinone with Indole and* 2-*Methylindole.*—Indole (0·4 g.) and 1 : 4-naphthaquinone (0·6 g.) were dissolved in acetic acid (20 c.c.) and left at room temperature. After 7 days, the red needles which had separated were collected and recrystallised from nitrobenzene. 2 : 3-*Di*-(1 : 4-*naphthaquinon*-2-*yl*)*indole* (XIV) formed brilliant scarlet needles, m. p. 356—360° (decomp.), very sparingly soluble in all the usual solvents, giving orange solutions (Found : C, 78·6; H, 3·6; N, 3·3. $C_{28}H_{15}O_4N$ requires C, 78·3; H, 3·5; N, 3·3%). When boiled with sodium hydroxide solution, the compound was slowly decomposed with the liberation of indole. Reduction with sodium dithionite gave a solution with a marked yellow fluorescence. Light absorption in acetone : Max., 3270, 3820, and 4800 A.; ε = 8800, 9000, and 4100, respectively.

The reddish-violet acetic acid mother-liquor was diluted with water (10 c.c.) and kept overnight, and the precipitate collected and twice recrystallised from ethanol. 2-3′-*Indolyl*-1 : 4-*naphthaquinone* formed glittering violet plates with a metallic lustre, m. p. 176° (Found : C, 78·8; H, 4·1; N, 5·3. $C_{18}H_{11}O_2N$ requires C, 79·2; H, 4·1; N, 5·1%). Its solutions in ethanol, acetone, and acetic acid were violet-red. Light absorption in ethanol : Max., 2175, 2830, and 5040—5090 A.; ε = 27,600, 21,550, and 7350, respectively. The diquinone (XIV) was obtained in higher yield as the only product when indole (0·6 g.) and 1 : 4-naphthaquinone (2 g.) in acetic acid (30 c.c.) were refluxed for 2 hours. After cooling, the product, most of which had separated during the heating, was collected and purified as above.

2-Methylindole (0·65 g.) and 1 : 4-naphthaquinone (1·6 g.) were refluxed for 5 hours in ethanol (30 c.c.) containing acetic acid (5 c.c.). 2-2′-*Methyl*-3′-*indolyl*-1 : 4-*naphthaquinone* separated on cooling of the violet solution, and after collection and recrystallisation from nitrobenzene formed very deep violet prisms, m. p. 176—178° (Found : C, 79·1; H, 5·5; N, 4·9. $C_{19}H_{13}O_2N$ requires C, 79·4; H, 5·5; N, 4·9%). Light absorption in ethanol : Max., 2450, 2800, and 5350 A.; ε = 15,100, 16,500, and 3710, respectively.

Reaction of 1 : 4-*Naphthaquinone with* 5 : 6-*Dihydroxy*-1-*methylindole.*—(*a*) The indole (0·2 g.) was dissolved in 20% acetic acid (10 c.c.), and a solution of the quinone (0·3 g.) in acetic acid (5 c.c.) was added. The mixture became violet, and the product soon began to separate. After 24 hours it was collected and recrystallised from ethanol, forming deep violet needles, m. p. 290—293° (decomp.) (Found : C, 71·6; H, 4·1. $C_{19}H_{13}O_4N$ requires C, 71·2; H, 4·1%). 2-(5 : 6-*Dihydroxy*-1-*methyl*-3-*indolyl*)-1 : 4-*naphthaquinone* was soluble in the common organic solvents, giving blue-violet solutions; in aqueous sodium hydroxide it gave a transient blue colour. Light absorption in ethanol : Max., 2870, 3020, and 5450 A.; ε = 21,500, 22,060, and 7050, respectively.

(*b*) 5 : 6-Dihydroxy-1-methylindole (0·1 g.) and 1 : 4-naphthaquinone (0·3 g.) were refluxed in acetic acid (8 c.c.) for 2 hours. The product separated during the heating and was filtered off hot from

the violet solution. After recrystallisation from nitrobenzene, 5 : 6-*dihydroxy*-1-*methyl*-2 : 3-*di*-(1 : 4-*naphthaquinon*-2-*yl*)*indole* (Found : C, 70·4; H, 3·5; N, 4·5. $C_{32}H_{17}O_6N,C_6H_5O_2N$ requires C, 70·2; H, 3·7; N, 4·7%) formed brownish-red needles (containing one molecule of solvent) which decomposed without melting at 345° and were very sparingly soluble in organic solvents to give an orange colour.

Reaction of p-*Benzoquinone with* 2-*Methyl*-5 : 6-*methylenedioxyindole*.—The indole (0·35 g.) and *p*-benzoquinone (0·43 g.) in ethanol (10 c.c.) containing acetic acid (1 c.c.) were boiled under reflux for 2 hours and the product, which crystallised overnight, was collected and recrystallised from benzene. 2-(2-*Methyl*-5 : 6-*methylenedioxy*-3-*indolyl*)-1 : 4-*benzoquinone* formed deep violet prisms, m. p. 191° (decomp.), and gave violet solutions in the common organic solvents (Found : N, 4·8. $C_{16}H_{11}O_4N$ requires N, 5·0%).

Reaction of p-*Benzoquinone with Scatole and* 2 : 3-*Dimethylindole*.—A solution of scatole (1·3 g.) and *p*-benzoquinone (1·1 g.) in acetic acid (30 c.c.) rapidly became reddish-violet. After 24 hours, the precipitate, which was a mixture of greyish prisms (the required product) and dark greenish-black needles (quinhydrone), was collected, washed with ethanol, and extracted with boiling water to remove the quinhydrone. The residue was twice recrystallised from nitrobenzene, and the *substance* formed colourless plates, m. p. 250—252°, very sparingly soluble in all organic solvents and unaffected by aqueous alkali (Found : C, 78·1; H, 5·5; N, 7·4. $C_{24}H_{20}O_2N_2$ requires C, 78·3; H, 5·4; N, 7·4%). When this was refluxed with acetic acid–acetic anhydride (1 : 1) the *diacetyl* derivative, colourless plates (from nitrobenzene), m. p. 360°, was obtained (Found : C, 74·2; H, 5·3; N, 6·2. $C_{28}H_{24}O_4N_2$ requires C, 74·3; H, 5·3; N, 6·2%). Similar treatment of 2 : 3-dimethylindole (4·2 g.) and *p*-benzoquinone (3 g.) in acetic acid (100 c.c.) gave a *substance* which, after recrystallisation (nitrobenzene), formed colourless plates, m. p. 345—348° (Found : C, 78·6; H, 5·9; N, 6·9. $C_{26}H_{24}O_2N_2$ requires C, 78·8; H, 6·1; N, 7·1%); its *diacetyl* derivative, prepared as above, separated from nitrobenzene as colourless plates, m. p. 352—354° (Found : C, 74·6; H, 5·7; N, 5·8. $C_{30}H_{28}O_4N_2$ requires C, 75·0; H, 5·8; N, 5·8%).

4 : 5-*Dimethylcatechol*.—*o*-4-Xylenol (15 g.) was dissolved in a solution of sodium hydroxide (25 g.) in water (1 l.). Potassium persulphate (30 g.) was added, and the mixture stirred at 35° until all was dissolved. After 4 days, the dirty brown solution was saturated with carbon dioxide and then extracted with ether (3 × 100 c.c.) to remove unchanged xylenol. The aqueous solution was acidified with hydrochloric acid, boiled for 0·5 hour, kept overnight, then decanted from tar and extracted with ether (3 × 150 c.c.). The ether was removed, and the residue extracted with water (50 c.c.) at 50°, filtered through charcoal, and evaporated to dryness. The residual gum was sublimed in a vacuum, giving colourless needles of 4 : 5-dimethylcatechol (1·8 g.), m. p. 80—82°.

4 : 5-*Dimethyl*-1 : 2-*benzoquinone*.—4 : 5-Dimethylcatechol (1 g.) was dissolved in dry ether (100 c.c.) and shaken for 20 minutes with silver oxide (4 g.) and anhydrous sodium sulphate (5 g.). The solids were removed by filtration, and the orange filtrate was concentrated to 10 c.c. When the concentrate was kept at 0°, the quinone separated as long orange needles, m. p. 101—102°. It was very much more stable than *o*-benzoquinone and could be kept for 2 months in the dark with little decomposition.

5 : 6-*Methylenedioxyindole*-2-*carboxylic Acid*.—This was prepared precisely as described by Lions and Spruson, *J. Proc. Roy. Soc. N.S.W.*, 1932, **66**, 171, for the 5 : 6-dimethoxy-analogue. *Ethyl* 5 : 6-*methylenedioxyindole*-2-*carboxylate* separated from ethanol as small yellowish prisms, m. p. 180° (Found : C, 70·0; H, 4·9. $C_{13}H_{11}O_4N$ requires C, 61·9; H, 4·7%), and the *acid* formed colourless plates, m. p. 250—251° (efferv.), from benzene (Found : C, 58·6; H, 3·5. $C_{10}H_7O_4N$ requires C, 58·5; H, 3·4%).

The authors thank Dr. R. Pitt-Rivers for a gift of tyrosylglycine.

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153. *The Chemistry of Adrenochrome. Part II. Some Analogues and Derivatives.*

By JOHN D. BU'LOCK and JOHN HARLEY-MASON.

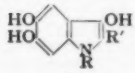
The oxidation of three adrenaline analogues, noradrenaline, α-methylnoradrenaline, and *N*-*iso*propylnoradrenaline, is described. With potassium iodate these compounds are converted into red crystalline iodoquinones which are isomerised on treatment with acetic anhydride–pyridine and give acetylated 3 : 5 : 6-trihydroxy-2-iodoindoles from which the iodine atom can be removed by reduction. Hydrolysis then yields yellow, intensely fluorescent 3 : 5 : 6-trihydroxyindoles. The iodo-quinones may also be isomerised by zinc acetate. Oxidation with potassium ferricyanide was also examined.

An explanation is advanced of the fact that adrenaline analogues containing a primary amino-group do not give a green fluorescence on autoxidation in alkaline solution.

The oxidation of adrenaline and its analogues in strongly acid solutions is discussed.

THE conversion of adrenaline *via* adrenochrome into 3 : 5 : 6-trihydroxy-1-methylindole (I; R = Me, R′ = H) has been described by one of us (Harley-Mason, *J.*, 1950, 1276; regarded as

Part I of this series), and we have now extended this work by examination of the oxidation of three analogues, namely noradrenaline (" Arterenol "), α-methylnoradrenaline (" Corbasil "), and *N-iso*propylnoradrenaline (" Aleudrine "). Adrenochrome can readily be prepared pure by oxidation of adrenaline with silver oxide in methanol containing formic acid as described in Part I: this process however failed with the three analogues, giving deep-red solutions from which no crystalline product could be obtained. In aqueous solution *N-iso*propylnoradrenaline was readily oxidised by silver oxide to a deep-red solution resembling that of adrenochrome, but noradrenaline and its α-methyl derivative gave dirty reddish-brown solutions from which no product could be isolated. Eventually it was found that the most satisfactory oxidising agent was potassium ferricyanide buffered with sodium hydrogen carbonate in aqueous solution. A solution of the quinone (II; R = Pr^i, R′ = H) so obtained from *N-iso*propylnoradrenaline gave with semicarbazide an orange crystalline semicarbazone and, on treatment with alkali, a deep-yellow solution with a strong green fluorescence. On cautious acidification of this solution with acetic acid a yellow amorphous precipitate was at first obtained, followed by separation of 3 : 5 : 6-trihydroxy-1-*iso*propylindole (I; R = Pr^i, R′ = H) as small yellow prisms.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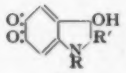
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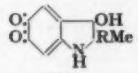
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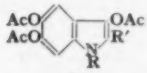
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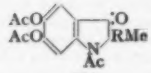

(V.)

On the other hand, the less stable solutions of the quinones (II; R = R′ = H) and (II; R = H, R′ = Me), obtained by similar oxidation of noradrenaline and α-methylnoradrenaline, gave on addition of alkali a yellowish-brown coloration but no fluorescence. A semicarbazone was obtained from (II; R = H, R′ = Me), but not from (II; R = R′ = H).

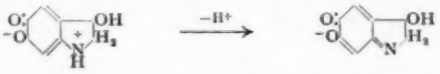
The action of aqueous potassium iodate on adrenaline salts gives 2-iodoadrenochrome (Blaschko and Richter, *J.*, 1937, 601) and we have now found that similar iodo-quinones, namely 2-iodo-1-*iso*propylnoradrenochrome (II; R = Pr^i, R′ = I), 2-iodo-2-methylnoradrenochrome (III; R = I) and 2-iodonoradrenochrome (II; R = H, R′ = I) can be obtained from *N-iso*propyl-, α-methyl-, and noradrenochrome respectively, though in poor yield. Since it was found (Part I, *loc. cit.*) that the action of pyridine and acetic anhydride on adrenochrome resulted in rearrangement as well as acetylation, the action of these reagents on the iodo-quinones was investigated From 2-iodoadrenochrome and from (II; R = Pr^i, R′ = I), 3 : 5 : 6-triacetoxy-2-iodo-1-methylindole (IV; R = Me, R′ = I) and 3 : 5 : 6-triacetoxy-2-iodo-1-*iso*propylindole (IV; R = Pr^i, R′ = I), respectively, were readily obtained in high yield. With (II; R = H, R′ = I) and (III; R = I), *N*-acetylation also occurred, giving 3 : 5 : 6-triacetoxy-1-acetyl-2-iodoindole (IV; R = Ac, R′ = I) and 5 : 6-diacetoxy-1-acetyl-2 : 3-dihydro-2-iodo-3-keto-2-methylindole (V; R = I).

Treatment of the iodo-indoles thus obtained with zinc dust and acetic acid removed the iodine atom. The product (IV; R = Me, R′ = H) from (IV; R = Me, R′ = I) was identical with that obtained directly from adrenochrome. From the alkaline hydrolysis of (IV; R = Ac, R′ = H) and (V; R = H) it was hoped to obtain the dihydroxyindoxyls (I; R = R′ = H) and (I; R = H, R′ = Me); unfortunately both products were very soluble in water and isolation from the small amount of starting material available proved unsuccessful. There can be little doubt, however, that these products were formed, since the yellow solutions displayed the intense green fluorescence characteristic of dihydroxyindoxyls, and, further, the solution obtained from (IV; R = Ac, R′ = H) on acidification and exposure to air slowly deposited a black precipitate whose solution in alkali showed the intense permanganate colour characteristic of tetrahydroxyindigo (Harley-Mason, *J.*, 1948, 1244). The solution obtained from (V; R = H), containing the indoxyl (I; R = H, R′ = Me) in which the 2-position is blocked by a methyl group thus preventing indigo formation, turned dark brown on similar oxidation, but gave no precipitate.

The isomerisation of adrenochrome to 3 : 5 : 6-trihydroxy-1-methylindole by the action of zinc acetate has been described by Fischer, Derouaux, Lambot, and Lecomte (*Bull. Soc. chim. Belg.*, 1950, **59**, 72). We have applied a similar procedure to the iodo-quinones; the action of zinc acetate on 2-iodoadrenochrome and 2-iodo*iso*propylnoradrenochrome followed by sodium dithionite leads directly to the formation, though in rather poor yield, of the dihydroxyindoxyls (I; R = Me, R′ = H) and (I; R = Pr^i, R′ = H), the iodine atom being removed by the reducing agent. 2-Iodonoradrenochrome on similar treatment gave a yellow, strongly fluorescent solution, but the indoxyl could not be isolated. 2-Iodo-2-methylnoradrenochrome gave a yellowish-brown solution which was non-fluorescent, so that evidently the indoxyl was

not formed, probably because isomerisation of (II; R = H, R′ = I) to the iodo-indoxyl would involve the migration of two hydrogen atoms both from the secondary alcohol group in the 3-position, whereas in all the other cases the migration involves one hydrogen atom each from the 2- and the 3-position.

The detection and estimation of small amounts of adrenaline by means of the green fluorescence developed when alkaline solutions are allowed to autoxidise has been described by several authors (Paget, *Bull. Sci. Pharmacol.*, 1930, **37**, 357; Gaddum and Schild, *J. Physiol.*, 1934, **80**, 9P; Ehrlén, *Farm Revy.*, 1948, **37**, 242). That the compound responsible for the fluorescence is the indoxyl (I; R = Me, R′ = H), formed by oxidation of the adrenaline to adrenochrome followed by isomerisation, has been argued earlier (Part I, *loc. cit.*; Ehrlén, *loc. cit.*). Bacq, Fischer, and Lecomte (*Arch. internat. Physiol.*, 1949, **56**, 380) have examined the specificity of this reaction and by a comparative study of adrenaline analogues have shown that a fluorescence is given only by *N*-alkyl analogues. It is evident from our result that even in the absence of a substituent on the nitrogen atom, the corresponding quinone is formed on oxidation, so that failure to give a fluorescence must depend on the subsequent isomerisation following a different course. From noradrenaline the quinone (II; R = R′ = H) is formed on oxidation.

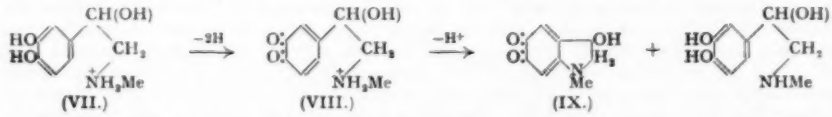
(IIa.)  (VI.)

By analogy with adrenochrome, the zwitterionic mesomeric structure (II*a*) must make a large contribution (cf. Harley-Mason, *Experientia*, 1948, **4**, 307), so that the most probable reaction with alkali will be removal of a proton from the nitrogen atom, giving the anion (VI). Since this anion is a dihydrohydroxyindole derivative, it would not be expected to show the fluorescence characteristic of an indoxyl. An isomerisation of this kind is of course not possible in the cases of quinones derived from adrenaline and similar *N*-alkylated compounds, since these contain no hydrogen attached to the nitrogen atom.

In Part I (*loc. cit.*) the preparation of aqueous solutions of adrenochrome by oxidation of adrenaline with buffered persulphate was described. We have now found that oxidation with potassium ferricyanide in the presence of sodium hydrogen carbonate proceeds very much more rapidly, and better yields of products are obtained

The oxidation of adrenaline with lead dioxide at pH 0—1 has been investigated by Rangier (*Compt. rend.*, 1945, **220**, 246) and Ruiz-Gijon (*Nature*, 1950, **166**, 831). Both authors have suggested that under these conditions the orange-yellow solution obtained contains the adrenaline quinone (2-hydroxy-2-3′ : 4′-quinonylethylmethylamine), since reduction leads to the re-formation of adrenaline. We have confirmed these observations and also found that when an alkaline buffer, such as sodium acetate or hydrogen carbonate, is added to the orange-yellow solution (after removal of excess of oxidising agent) the colour at once changes irreversibly to the deep red of adrenochrome. The red colour can then be intensified by the addition of more oxidising agent.

These phenomena may be explained as follows : In strongly acid solution the adrenaline will be present entirely as the cation (VII), which on oxidation will give the quinone (VIII), having the orange-yellow colour usual in *o*-quinones. While the nitrogen atom retains its positive


(VII.) (VIII.) (IX.)

charge, cyclisation does not occur since this involves anionoid attack by the nitrogen on the 6-position of the quinonyl group. When the hydrogen-ion concentration is reduced, the free amine is formed, and cyclisation then occurs to give the deep-red adrenochrome (IX), half of the original quinone being reduced back to adrenaline. Addition of further oxidising agent at this point converts the adrenaline directly to adrenochrome, thus intensifying the colour.

The oxidation of several other (dihydroxyphenyl)ethylamine derivatives, namely noradrenaline, α-methylnoradrenaline, *N-iso*propylnoradrenaline, 2-(3 : 4-dihydroxyphenyl)ethylamine, 2-(3 : 4-dihydroxyphenyl)ethylmethylamine, and 3 : 4-dihydroxyphenylalanine, under the same strongly acidic conditions has also been examined. The same result was obtained in all cases; the orange-yellow quinone was formed and on subsequent addition of an alkaline buffer the deep-red, cyclised quinone was at once obtained.

As the quinones cyclised at once at pH less than about 2, it is unlikely that they are formed as stable entities under biological conditions unless cyclisation is prevented in some other way.

Experimental.

Oxidations with Potassium Ferricyanide.—Adrenaline (1·8 g., 0·01 mol.) was suspended in water (30 c.c.) and acetic acid added dropwise with shaking until all the solid had dissolved. A solution of potassium ferricyanide (13 g., 0·04 mol.) and sodium hydrogen carbonate (4·2 g., 0·05 mol.) in water (70 c.c.) was added with stirring. A brisk effervescence of carbon dioxide occurred, and after 5 minutes, the deep-red adrenochrome solution was treated with 10% sodium hydroxide solution (10 c.c.), giving a deep-yellow solution having a strong, green fluorescence. The solution was then acidified with acetic acid and kept overnight at 0°, a little sodium dithionite being added to prevent oxidation. The 3 : 5 : 6-trihydroxy-1-methylindole monohydrate (1·2 g.), which had separated as small yellow prisms, m. p. 230—232°, was then collected.

Oxidation of *N-iso*propylnoradrenaline sulphate (1·0 g., 0·004 mol.) in the same manner similarly gave a deep-red solution. After addition of alkali, the acidification with acetic acid was performed very slowly; at first a yellow amorphous precipitate separated, and this was filtered off and discarded. Further addition of acetic acid to the filtrate gave 3 : 5 : 6-*trihydroxy*-1-iso*propylindole* (0·3 g.) as very small, yellow nodules, m. p. 214—216° (decomp.) (Found : C, 63·2; H, 6·1; N, 6·8. $C_{11}H_{11}O_3N$ requires C, 63·7; H, 6·3; N, 6·75%). The product was sparingly soluble in water and organic solvents, giving bright yellow solutions showing a strong green fluorescence. Acid solutions rapidly absorbed oxygen from the air giving a black precipitate which dissolved in alkali to an intense permanganate coloured solution, and was thus probably 5 : 6 : 5′ : 6′-tetrahydroxy-*NN*′-di*iso*propylindigo. To a portion of the red solution obtained in the original oxidation, semicarbazide hydrochloride and sodium acetate were added After 24 hours, the N-iso*propylnoradrenochrome semicarbazone*, which had crystallised, was collected and recrystallised from water, giving orange-red plates, m. p. 204° (decomp.) (Found : N, 21·0. $C_{12}H_{14}O_3N_4$ requires N, 21·2%).

Similar oxidation of α-methylnoradrenaline hydrochloride (0·65 g., 0·003 mol.) gave a red solution which on treatment with alkali gave a deep yellow-brown colour, but no fluorescence. Addition of acetic acid gave a light-brown precipitate which could not be purified. Addition of semicarbazide hydrochloride and sodium acetate to the red solution gave 2-*methylnoradrenochrome semicarbazone*, forming orange-yellow needles, m. p. 195—196° (decomp.), from water (Found : N, 23·8. $C_{10}H_{12}O_3N_4$ requires N, 23·7%).

Similar oxidation of noradrenaline hydrochloride (0·6 g., 0·003 mol.) produced a red solution which decomposed rapidly giving a dark precipitate. Addition of alkali gave no fluorescence, and no semicarbazone could be prepared from the original red solution.

Preparation of Iodo-quinones.—A solution of *N-iso*propylnoradrenaline sulphate (1·5 g.) in water (50 c.c.) was treated at 0° with a solution of potassium iodate (1·2 g.) in water (50 c.c.). A brown, rather tarry precipitate soon began to separate; this was filtered off and discarded, and more tarry material was similarly removed until, after 2 hours, crystals began to form. The mixture was kept overnight at 0° and the reddish-brown needles of 2-*iodo*-N-iso*propylnoradrenochrome* (II; R = Pr^i, R′ = I) *hemihydrate* (0·5 g.) were then collected (Found : C, 38·6; H, 4·6. $C_{11}H_{12}O_3NI,0{\cdot}5H_2O$ requires C, 38·6; H, 3·8%).

Noradrenaline hydrochloride (1 g.) was similarly treated with potassium iodate (1 g.). After 2 hours a large amount of black amorphous material was filtered off and the filtrate kept 24 hours at 0°. The product, 2-*iodonoradrenochrome* (II; R = H, R′ = I) (0·25 g.), separated as compact dark-red, almost black, prisms (Found : C, 32·9; H, 2·2; I, 43·0. $C_9H_6O_3NI$ requires C, 33·0; H, 2·1; I, 43·6%).

α-Methylnoradrenaline hydrochloride (1 g.) was similarly treated with potassium iodate (1·1 g.). Some orange, amorphous material was filtered off after 1 hour and the filtrate kept for 6 hours at 0°, after which the crystalline product (0·7 g.) was collected. 2-*Iodo*-2-*methylnoradrenochrome* (III; R = Me, R′ = I) formed deep-red needles (Found : C, 34·8; H, 3·0; N, 4·5. $C_{10}H_8O_3NI$ requires C, 35·4; H, 2·6; N, 4·6%). When heated, all three iodo-quinones decomposed indefinitely without melting. (II; R = Pr^i, R′ = I) and (II; R = H, R′ = I) decomposed rapidly on storage : (III; R = I) was, however, more stable.

Acetylation of the Iodo-quinones.—The iodo-quinones were dissolved in a mixture of pyridine (5 c.c.) and acetic anhydride (5 c.c.) and the solution kept for 24 hours at room temperature. The mixture was then poured into water, and the separated solid collected and recrystallised from aqueous ethanol (charcoal). From 2-iodo-*N-iso*propylnoradrenochrome (0·4 g.) there was thus obtained 3 : 5 : 6-*triacetoxy*-2-*iodo*-1-iso*propylindole* (IV; R = Pr^i, R′ = I) (0·45 g.), prisms, m. p. 163—164° (Found : C, 44·7; H, 4·1; N, 3·2; I, 26·6. $C_{17}H_{16}O_6NI$ requires C, 44·5; H, 3·9; N, 3·05; I, 27·6%).

2-Iodonoradrenochrome (0·3 g.) gave 3 : 5 : 6-*triacetoxy*-1-*acetyl*-2-*iodoindole* (IV; R = Ac, R′ = I) (0·33 g.), prisms, m. p. 208—209° (Found : C, 42·2; H, 3·0. $C_{16}H_{14}O_7NI$ requires C, 41·8; H, 3·1%).

2-Iodo-2-methylnoradrenochrome (0·4 g.) gave 5 : 6-*diacetoxy*-1-*acetyl*-2 : 3-*dihydro*-2-*iodo*-3-*keto*-2-*methylindole* (V; R = I) (0·3 g.), as pale yellow prisms, m. p. 199—200° (Found : C, 42·1; H, 3·4. $C_{15}H_{14}O_6NI$ requires C, 41·7; H, 3·2%)

2-Iodoadrenochrome (0·5 g.) gave 3 : 5 : 6-*triacetoxy*-2-*iodo*-1-*methylindole* (IV; R = Me, R′ = I) (0·6 g.), prisms, m. p. 150° (Found : C, 42·1; H, 3·5. $C_{15}H_{14}O_6NI$ requires C, 41·7; H, 3·2%).

De-iodination of the Acetylated Iodo-derivatives.—The acetylated iodo-compounds were dissolved in boiling acetic acid (4 c.c.), and zinc dust (2 g.) added slowly over a period of 15 minutes. The solution was then decanted from excess of zinc and poured into water. After some time at 0°, the separated solid was

collected and recrystallised. From 3 : 5 : 6-triacetoxy-1-acetyl-2-iodoindole (0·3 g.) there was obtained 3 : 5 : 6-*triacetoxy*-1-*acetylindole* (IV; R = Ac, R′ = H) (0·15 g.), m. p. 125—127° (needles from aqueous ethanol) (Found: C, 57·2; H, 4·5. $C_{16}H_{15}O_7N$ requires C, 57·6; H, 4·5%). 5 : 6-Diacetoxy-1-acetyl-2 : 3-dihydro-2-iodo-3-keto-2-methylindole (0·3 g.) gave 5 : 6-*diacetoxy*-1-*acetyl*-3-*hydroxy*-2-*methylindole* (V; R = H) (0·13 g.), m. p. 185—187° (prisms from benzene–light petroleum) (Found: C, 59·4; H, 5·1. $C_{16}H_{15}O_6N$ requires C, 59·0; H, 4·9%). 3 : 5 : 6-Triacetoxy-2-iodo-1-methylindole (0·5 g.) gave 3 : 5 : 6-triacetoxy-1-methylindole (IV; R = Me; R′ = H) (0·32 g.), m. p. 113°. The corresponding *iso*propyl analogue gave a gum which crystallised when kept for 3 months; recrystallisation from aqueous ethanol gave 3 : 5 : 6-*triacetoxy*-1-iso*propylindole*, m.p. 87° (Found: C, 61·4; H, 5·7. $C_{17}H_{19}O_6N$ requires C, 61·3; H, 5·7%).

Hydrolysis of the Acetyl Derivatives.—3 : 5 : 6-Triacetoxy-1-acetylindole (0·1 g.) was boiled for 1 hour under nitrogen with 2N-sodium hydroxide (4 c.c.). The solid slowly dissolved giving a yellow solution with an intense green fluorescence. When cool the solution was acidified with acetic acid, but no solid separated even after some while at 0°, and attempts to extract the indoxyl with organic solvents were unsuccessful. After exposure to air for some time, the fluorescence slowly disappeared and a black precipitate separated; this dissolved in aqueous alkali to an intense permanganate-coloured solution.

The triacetyl compound (V; R = H) (0·1 g.) on similar treatment also gave a yellow solution with an intense green fluorescence. Attempts to isolate the indoxyl were similarly unsuccessful.

Isomerisation of Iodoquinones with Zinc Acetate.—2-Iodoadrenochrome (0·5 g.) was stirred with water (10 c.c.), and 20% zinc acetate solution (5 c.c.) added. After 10 minutes' stirring the red colour of the solution had changed to yellow with a green fluorescence. Sodium dithionite (0·2 g.) was then added, the mixture warmed to 60°, and some dark solid which remained undissolved was filtered off. When kept at 0°, the filtrate deposited 3 : 5 : 6-trihydroxy-1-methylindole monohydrate (0·1 g.). Similarly *N*-*iso*propyl-2-iodonoradrenochrome gave a very small yield of 3 : 5 : 6-trihydroxy-1-*iso*propylindole. 2-Iodonoradrenochrome gave a yellow, fluorescent solution, but no solid product could be isolated. 2-Iodo-2-methylnoradrenochrome gave a brownish-yellow solution which was non-fluorescent.

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UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, November 24th*, 1950.]

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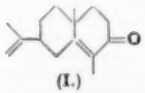
154. *The Structure of β-Cyperone.*

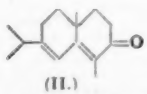
By F. J. McQUILLIN.

By comparison of the ultra-violet absorption of their derivatives, the sesquiterpene ketones α- and β-cyperone are shown to be structural isomers (I) and (II) and not stereoisomeric forms of structure (I) as proposed by Bradfield, Pritchard, and Simonsen (*J.*, 1937, 760).

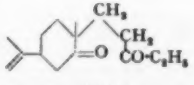
α-CYPERONE, a sesquiterpene ketone, $C_{15}H_{22}O$, isolated from the tubers of *Cyperus rotundus* (Hegde and Rao, *J. Soc. Chem. Ind.*, 1935, **54**, 387T: Bradfield, Hegde, Rao, Simonsen, and Gillam, *J.*, 1936, 667) was shown to possess the structure (I) (Bradfield *et al.*, *loc. cit.*; Bradfield, Pritchard, and Simonsen, *J.*, 1937, 760). A synthetic ketone, obtained by cyclisation of an intermediate (III) by means of sodium ethoxide, was found to be very closely similar to α-cyperone and to give closely similar derivatives (Adamson, McQuillin, Robinson, and Simonsen, *J.*, 1937, 1576).



(I.)



(II.)



(III.)

On digestion with acid or with alkali, α-cyperone is converted into an isomeric ketone (known as β-cyperone) of larger molecular refraction and optical rotation. Cyclisation of the diketone (III) by means of 50% sulphuric acid led to a synthetic ketone yielding derivatives generally similar to those of β-cyperone; the ketone itself, however, showed distinctly higher refraction and optical rotation (Adamson, McQuillin, Robinson, and Simonsen, *loc. cit.*).

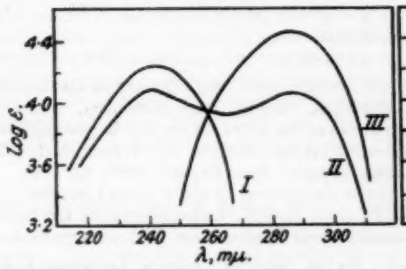
The semicarbazones of α- and β-cyperone were found by Bradfield, Pritchard, and Simonsen (*loc. cit.*) to yield on ozonolysis the same main degradation product, $C_{15}H_{23}O_4N_3$, and these authors concluded that "the two ketones must presumably be stereo-isomerides, differing in the disposition of the angle methyl and the *iso*propenyl group." The physical properties of

α-cyperone and β-cyperone, obtained by isomerisation and synthetically, are, however, at variance with this conclusion:

α-Cyperone	n_D^{25} 1·5283	$[R_L]_D$ 67·5	$[\alpha]_{5461}$ + 138°
β-Cyperone, "*N*"	1·5414	68·9	+ 239°
" "*B*"	1·5565	70·5	+ 111·7°
" "*O*"	n_D^{16} 1·5590	70·4	+ 342°

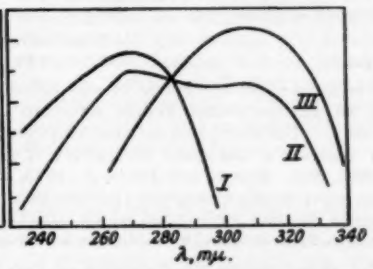
β-Cyperone "*N*" refers to the ketone from isomerisation of natural α-cyperone; "*B*" and "*O*" designate the synthetic specimens prepared by Adamson, McQuillin, Robinson, and Simonsen (*loc. cit.*).

FIG. 1.
Oximes of α- and β-Cyperones.



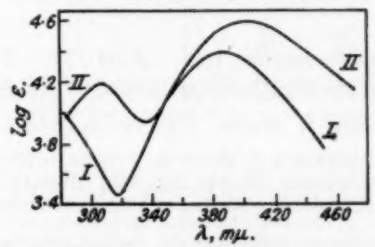
Curve I—α-cyperone oxime. Curve II—β-cyperone oxime from isomerisation. Curve III—oxime of synthetic β-cyperone.

FIG. 2.
Semicarbazones of α- and β-Cyperones.



Curve I—semicarbazone of α-cyperone. Curve II—semicarbazone of β-cyperone from isomerised α-ketone. Curve III—semicarbazone of synthetic β-cyperone.

FIG. 3.
2 : 4-Dinitrophenylhydrazones of α- and β-cyperones.



Curve I—2 : 4-dinitrophenylhydrazone of α-cyperone.
Curve II—2 : 4-dinitrophenylhydrazone of β-cyperone from isomerisation of α-cyperone.

α-Cyperone shows the exaltation of molecular refraction to be expected of structure (I), $[R_L]_D$ calc. 66·15, whilst β-cyperone and particularly the synthetic specimens show values greatly in excess of those to be expected of a stereoisomer of (I). These properties were thought to indicate for β-cyperone a structure (II) (cf. McQuillin, *Chem. and Ind.*, 1937, **56**, 514) which is *a priori* likely to result from acid or alkali-catalysed inversion at the centre carrying the *iso*propenyl group. Structure (II) is, however, consistent with Bradfield, Pritchard, and Simonsen's oxidation results (*loc. cit.*) only if the β-ketone and its semicarbazone prepared by these authors is regarded as a mixture containing a high proportion of the α-ketone from which the characteristic ozonolysis product was derived.

An examination of the ultra-violet absorption of the oximes, semicarbazones, and 2 : 4-dinitrophenylhydrazones of α- and β-cyperone has now shown this to be the case. The oxime and semicarbazone derived from the β-ketone made by isomerisation of natural α-cyperone show double absorption maxima (Figs. 1 and 2). The absorption peak at shorter wave-lengths corresponds with that shown by the corresponding derivative of α-cyperone and the longer-wave-length maximum with that of the derivative of the pure β-isomer obtained synthetically.

These results are in good agreement with the physical properties of the β-ketones noted above, and from inspection of the absorption curves it is clear that the β-semicarbazone used for ozonolysis by Bradfield, Pritchard, and Simonsen (*loc. cit.*) contained a sufficiently large proportion of the α-derivative to account for the isolation of the oxidation product corresponding to the α-ketone. In the case of the 2 : 4-dinitrophenylhydrazones (Fig. 3) the curve for the β-isomer shows a general shift of some 18 mμ. towards longer wave-lengths, and this derivative clearly corresponds with an essentially pure β-isomer. The positions of the principal maxima are given below (solvent, ethyl alcohol).

Oximes:	$\lambda_{max.}$	log $\varepsilon_{max.}$	*Semicarbazones:*	$\lambda_{max.}$	log $\varepsilon_{max.}$
α-Cyperone	244 mμ.	4·25	α-Cyperone	270 mμ.	4·32
β-Cyperone, "*N*"	244	4·09	β-Cyperone, "*N*"	270	4·20
	286·5	4·05		308	4·09
β-Cyperone, synthetic "*O*" ...	286·5	4·47	β-Cyperone, synthetic "*O*"	307·5	4·45

2 : 4-*Dinitrophenylhydrazones:*

α-Cyperone	386	4·39	β-Cyperone, "*N*"	404	4·57

The ultra-violet absorption of α-cyperone has already been characterised as corresponding with an αβ-unsaturated ketone structure [Bradfield, Hegde, Rao, Simonsen, and Gillam (*loc. cit.*)]. The absorption maxima of the derivatives of the α-ketone are also in good agreement with values for analogous derivatives of αβ-unsaturated ketones (cf. Evans and Gillam, *J.*, 1943, 565; Braude and Jones, *J.*, 1945, 498; Braude, *Ann. Reports*, 1945, **42**, 105). The longer wave-length absorption characteristic of the derivatives of the β-ketone implies a more extended dienone conjugation which, apart from some drastic rearrangement of the molecule for which there is no evidence, can be accommodated only in structure (II) for β-cyperone.

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155. *Studies of Trifluoroacetic Acid. Part III. The Use of Trifluoroacetic Anhydride in the Synthesis of Aromatic Ketones and Sulphones.*

By E. J. BOURNE, M. STACEY, J. C. TATLOW, and J. M. TEDDER.

Trifluoroacetic anhydride is shown to promote, under mild conditions, the condensation between suitably activated aromatic compounds and carboxylic acids or sulphonic acids, to give ketones or sulphones, respectively.

THE discovery that trifluoroacetic anhydride can be employed to promote ester formation between hydroxy-compounds and carboxylic acids (Bourne, Stacey, Tatlow, and Tedder, *J.*, 1949, 2976) suggested that it might be possible to utilise this halogenated anhydride for the preparation of ketones directly from aromatic compounds and carboxylic acids. Monochloroacetic anhydride (Unger, *Annalen*, 1933, **504**, 267), aluminium chloride (Groggins, Nagel, and Stirton, *Ind. Eng. Chem.*, 1934, **26**, 1317), hydrogen fluoride (Simons, Randall, and Archer, *J. Amer. Chem. Soc.*, 1939, **61**, 1795), and phosphoric anhydride (Kosolapoff, *ibid.*, 1947, **69**, 1651; Hartough and Kosak, *ibid.*, p. 3098) have all been employed as condensing agents in this type of reaction.

The reactions now reported show that mixtures of trifluoroacetic anhydride and carboxylic acids give good yields of ketones from polyalkylbenzenes, phenyl ethers, furan, and thiophen, under mild conditions. Under similar conditions small yields of ketones were obtained from the xylenes, but there was no detectable reaction with benzene or toluene. The carboxylic acids employed were acetic, benzoic, and cinnamic acids.

In general, the aromatic compound (1 mol.) was added to a solution of the carboxylic acid (1—1·5 mols.) in trifluoroacetic anhydride (1·5—2·5 mols.) and left for a few hours, the reaction mixture being gently warmed (maximum, 60°) when necessary. The solution was then poured into aqueous sodium hydrogen carbonate and the ketone isolated by suitable solvent extraction. An attempt to effect the acetylation of toluene by the use of more drastic reaction conditions

(110° for 6 hours) led to considerable charring and still afforded little or no *p*-methylacetophenone.

In two experiments trifluoroacetic anhydride was replaced by heptafluorobutyric anhydride, but with this reagent the yield of *p*-methoxyacetophenone from anisole and acetic acid fell from about 80% to 18%, whilst toluene still could not be acetylated.

In a reaction analogous to the ketone synthesis, trifluoroacetic anhydride can be used for the production of sulphones from aromatic compounds and sulphonic acids, and *p*-methoxyphenyl *p*-tolyl sulphone and mesityl *p*-tolyl sulphone were thus prepared.

It seems probable that, in the above syntheses of ketones and sulphones, and also in the production of esters directly from carboxylic acids and hydroxy-compounds (Bourne, Stacey, Tatlow, and Tedder, *loc. cit.*), the trifluoroacetic anhydride functions by forming a mixed anhydride with the carboxylic acid or sulphonic acid in question. The mechanism of the reaction is now under investigation, and it is already evident that an equilibrium exists in the acid–anhydride system, since an acetic anhydride–trifluoroacetic acid mixture and an acetic acid–trifluoroacetic anhydride mixture show similar properties in that they both react (*a*) with hydroxy-compounds to give acetate esters (Bourne, Stacey, Tatlow, and Tedder, *loc. cit.*, and unpublished results), and (*b*) with suitably activated aromatic compounds to give methyl ketones [cf. Newman (*J. Amer. Chem. Soc.*, 1945, **67**, 345) who has shown that an acetic anhydride–trifluoroacetic acid mixture reacts with anisole to give *p*-methoxyacetophenone].

Experimental.

p-*Methoxyacetophenone.*—(*a*) Anisole (0·52 c.c.) was added to a mixture of trifluoroacetic anhydride (1·20 c.c.) and acetic acid (0·42 c.c.). After being kept at room temperature for 3 hours, the solution was poured into excess of sodium hydrogen carbonate solution and then exhaustively extracted with chloroform. The extracts were dried ($MgSO_4$), filtered, and evaporated to a syrup, which was distilled at 90—95° (bath-temp.)/0·001 mm. The distillate (0·56 g., 78%), crystallised from light petroleum (b. p. 40—60°), had m. p. 38°. Baranger (*Bull. Soc. chim.*, 1931, [iv], **49**, 1213) gave m. p. 38—39° for *p*-methoxyacetophenone.

(*b*) The experiment was repeated with the same quantities of reagents, but under different reaction conditions, as tabulated below. The product was isolated as its semicarbazone, m. p. 198—200° (Found: C, 57·7; H, 6·1. Calc. for $C_{10}H_{13}O_2N_3$: C, 58·0; H, 6·3%). Baranger (*loc. cit.*) recorded m. p. 202° for this compound.

Reaction temp. (± 2°)	18°	18°	18°	18°	2°	45°	75°
Reaction time (mins.)	10	20	40	150	150	150	150
Yield of semicarbazone (%)	37	64	66	81	57	69	57

(*c*) Anisole (0·26 c.c.) was added to a mixture of heptafluorobutyric anhydride (1·00 c.c.) and acetic acid (0·15 c.c.). The mixture was kept at 18° for 3 hours before being treated with sodium hydrogen carbonate solution as above. The product, isolated as its semicarbazone (0·09 g., 18%), had m. p. 198—199°.

p-*Ethoxyacetophenone.*—Phenetole (0·50 c.c.) was added to a mixture of acetic acid (0·40 c.c.) and trifluoroacetic anhydride (0·70 c.c.), and the mixture was kept at 21° for 3 hours. The solution was neutralised with aqueous sodium hydrogen carbonate and exhaustively extracted with chloroform. The extracts were dried ($MgSO_4$), filtered, and evaporated to yield a crystalline solid. Recrystallisation from light petroleum (b. p. 40—60°) afforded flat hexagonal plates (0·59 g., 89%), m. p. 36—37° (Found: C, 73·4; H, 7·5. Calc. for $C_{10}H_{12}O_2$: C, 73·1; H, 7·4%). The product gave a semicarbazone, m. p. 182°. Unger (*loc. cit.*) gave m. p. 37—38° for *p*-ethoxyacetophenone and m. p. 181·5° for its semicarbazone.

p-*Methoxybenzophenone.*—Benzoic acid (0·61 g.) was dissolved in trifluoroacetic anhydride (1·60 c.c.), and anisole (0·50 c.c.) was added. The reaction mixture was kept at 50—60° for 5 hours. The crude product, isolated as above, was crystallised from alcohol to give *p*-methoxybenzophenone (0·54 g., 56%), m. p. 62° (Found: C, 79·4; H, 5·5. Calc. for $C_{14}H_{12}O_2$: C, 79·2; H, 5·7%). Rennie (*J.*, 1882, **41**, 220) gave m. p. 61—62°.

ω-*Benzylidene*-p-*methoxyacetophenone.*—Anisole (0·50 c.c.) was added to a solution of cinnamic acid (0·74 g.) in trifluoroacetic anhydride (1·20 c.c.) and the mixture was warmed at 45° for 1 hour. Extracted as above, the crude ketone was distilled at 285° (bath-temp.)/15 mm. The distillate, recrystallised from alcohol, afforded ω-benzylidene-*p*-methoxyacetophenone (0·90 g., 82%), m. p. 106° (Found: C, 81·0; H, 6·0. Calc. for $C_{16}H_{14}O_2$: C, 80·7; H, 5·9%). Stockhausen and Gattermann (*Ber.*, 1892, **25**, 3536) gave m. p. 106—107°.

2 : 4 : 6-*Trimethylbenzophenone.*—Mesitylene (1·00 c.c.) was added to a solution of benzoic acid (0·99 g.) in trifluoroacetic anhydride (1·50 c.c.). The mixture was heated at 60° for 3 hours and the crude ketone was isolated as above. Distillation at 208—212° (bath-temp.)/15 mm. gave a viscous syrup (0·83 g., 52%) (Found: C, 85·4; H, 7·4. Calc. for $C_{16}H_{16}O$: C, 85·7; H, 7·2%). Nitration gave fine yellow needles, m. p. 203°. Fuson and Armstrong (*J. Amer. Chem. Soc.*, 1941, **63**, 2650) recorded b. p. 135—140°/4 mm. for 2 : 4 : 6-trimethylbenzophenone, and m. p. 202—204° for its trinitroderivative.

2-*Acetylthiophen.*—Thiophen (0·50 c.c.) was added to a solution of acetic acid (0·50 c.c.) in trifluoro-

acetic anhydride (1·00 c.c.) and the mixture was warmed at 40—50° for 1 hour. The crude ketone was isolated as above and converted directly into its semicarbazone. Recrystallised from water, the product (0·59 g., 50%) had m. p. 192° (Found : C, 46·2; H, 5·0. Calc. for $C_7H_9ON_3S$: C, 45·9; H, 5·0%). Steinkopf and Jaffé (*Annalen*, 1917, **413**, 333) gave m. p. 190—191° for 2-acetylthiophen semicarbazone.

2-*Acetylfuran*.—Acetic acid (0·50 c.c.) was mixed with trifluoroacetic anhydride (1·50 c.c.), and furan (0·50 c.c.) was added. After 1 hour at room temperature the crude ketone was isolated as above. Distillation at 75° (bath-temp.)/11 mm. afforded 2-acetylfuran (0·32 g., 43%), m. p. 29—30°. The ketone gave a semicarbazone, m. p. 147—148° (Found : C, 49·8; H, 5·5. Calc. for $C_7H_9O_2N_3$: C, 50·3; H, 5·4%). Bouveault (*Ber.*, 1901, **34**, 1072) gave m. p. 28·5° for the ketone and m. p. 148° for its semicarbazone.

p-*Methoxyphenyl* p-*Tolyl Sulphone*.—Toluene-*p*-sulphonic acid monohydrate (1·05 g.) was warmed with trifluoroacetic anhydride (3·5 c.c.) at 40° for 15 minutes before anisole (0·50 c.c.) was added. Heating was continued at 60—70° for 4 hours and the crude sulphone was isolated as above. Two recrystallisations from aqueous alcohol gave the sulphone (0·55 g., 46%), m. p. 103—104° (Found : C, 63·9; H, 5·5. Calc. for $C_{14}H_{14}O_3S$: C, 64·1; H, 5·4%). Burton and Hu (*J.*, 1948, 601) recorded m. p. 104—105° for this substance.

Mesityl p-*Tolyl Sulphone*.—Mesitylene (0·50 c.c.) was added to a solution of toluene-*p*-sulphonic acid monohydrate (0·89 g.) in trifluoroacetic anhydride (1·50 c.c.). The whole was heated at 50—60° for 4 hours and the crude sulphone was isolated in the manner already described. The pure product (0·64 g., 64%), m. p. 119—120°, was obtained by two crystallisations from light petroleum (b. p. 60—80°) (Found : C, 70·0; H, 6·6. Calc. for $C_{16}H_{18}O_3S$: C, 70·0; H, 6·6%). Meyer (*Annalen*, 1923, **433**, 327) reported m. p. 119° for mesityl *p*-tolyl sulphone.

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156. *The Constitution of Laminarin. Part II. The Soluble Laminarin of* Laminaria digitata.

By E. G. V. Percival and A. G. Ross.

Soluble laminarin, in distinction from the normal laminarin of *Laminaria cloustoni* (Part I, *J.*, 1950, 3494), requires precipitation by ethanol for isolation from acidified extracts of *L. digitata*. When isolated in this way it contains a small proportion (*ca.* 3%) of fucoidin which is reduced (to *ca.* 1%) only by electrodialysis. Methylation and subsequent hydrolysis indicates that soluble laminarin is constructed of β-D-glucopyranose units linked through $C_{(1)}$ and $C_{(3)}$, and the chain length determined from the yield of tetramethyl glucopyranose is *ca.* 20 units. On *X*-ray examination, the acetyl and methyl derivatives of the two forms are also almost indistinguishable and the molecular weights of the methylated derivatives appear to be of the same order.

Slight differences between normal and soluble laminarin are detectable on treatment with periodate, but soluble laminarin is only about one-third as reducing as normal laminarin towards hypoiodite. The reducing power increases, however, with the removal of fucoidin, but no satisfactory explanation can be advanced either for this phenomenon or for the difference in physical properties between the two forms.

From the common seaweed *Laminaria cloustoni*, the polysaccharide laminarin is liberated as an insoluble precipitate when the fronds are kept in acidulated water (see Part I, *J.*, 1950, 3494). *L. digitata*, however, differs in that the addition of a precipitant such as ethanol is necessary before the laminarin, which is exuded when this species is kept in dilute acid, is precipitated. Kylin (*Z. physiol. Chem.*, 1915, **96**, 337), among others, noted and studied this phenomenon and suggested that laminarin was a mixture of polymers of differing molecular sizes. Barry (*Sci. Proc. Roy. Dublin Soc.*, 1939, **22**, 59) re-investigated the problem and also expressed the opinion that the only difference between the soluble and insoluble forms of laminarin lay in the size of the calloidal particles and that only one laminarin occurs in seaweeds. In addition

Barry has pointed out (personal communication) that, by the addition of glycerol, the spontaneous precipitation of normal laminarin can be prevented and has suggested that the extract from *L. digitata* contains a substance which interferes with the aggregation of the colloidal molecules.

We have attempted to determine whether structural variations were responsible for this difference between the two forms of laminarin.

A comparison of the two specimens by the *X*-ray powder photography technique showed the presence of a diffuse band corresponding to a spacing of 2·2 A., but there was no apparent difference between the samples. For the acetylated and methylated derivatives, no obvious differences were detectable in such properties as specific rotation or specific viscosity.

When the fully methylated soluble laminarin was hydrolysed and the fragments analysed by quantitative paper chromatography and by separation on the cellulose column (see Part I, *loc. cit.*) the yield of tetramethyl glucopyranose (5·1%) corresponded to a chain length of about twenty glucose units, the main product of hydrolysis being 2 : 4 : 6-trimethyl glucose. This result is virtually indistinguishable from that previously reported for the laminarin of *L. cloustoni* (Part I, *loc. cit.*). The accompanying mixture of dimethyl glucoses (4·1%), although smaller in quantity than that isolated in the former experiments, owing to a modification of the conditions of hydrolysis, could, as in the former case, be accounted for very largely by the accompanying demethylation (2·9%) of the 2 : 4 : 6-trimethyl glucose, and the mixture consisted as before of 2 : 6- and 4 : 6-dimethyl glucoses.

It has not been possible as yet to determine precisely the molecular weight of methylated soluble laminarin but, estimated by the method of Caesar, Gruenhut, and Cushing (*J. Amer. Chem. Soc.*, 1947, **69**, 617), the value appears to lie between 2800 and 3800. This is similar to the value found for normal laminarin and in no way explains the difference in behaviour.

Oxidation with potassium periodate (Halsall, Hirst, and Jones, *J.*, 1947, 1399) liberated from soluble laminarin 1 mole of formic acid from 5·7 glucose residues, which is a slightly higher proportion than from the normal form, but the result cannot be evaluated in terms of structure because of the uncertainty as to the nature of the " reducing " terminal group of the chain. The yield of formaldehyde (1 mole/30 glucose units) was slightly lower than from normal laminarin (Part I, *loc. cit.*).

More marked, however, were the differences between the apparent chain lengths calculated from the reducing action on hypoiodite, the figures being 112 for soluble and 45 for normal laminarin. When the reducing power was estimated by the alkaline 3 : 5-dinitrosalicylate technique of Meyer *et al.* (*Helv. Chim. Acta*, 1948, **31**, 103) the value of 27 units for soluble laminarin was double that for normal laminarin. The results of this experiment, which involves heating with moderately concentrated alkali, must be taken with reserve since a progressive increase of reducing action on heating with alkali was found to take place with both forms. Thus the apparent chain length of normal laminarin estimated by the hypoiodite method fell to 17 after contact with sodium hydroxide (2N.) at 40° for 5 minutes and to 8 after 30 minutes at 65°.

Since, apart from the difference in reducing power, unexplained as yet, no obvious structural differences had been revealed to account for the physical differences exhibited by the two types of laminarin, another explanation was sought. The ash content of the spontaneously deposited laminarin is invariably low (*ca.* 0·2%) whereas that in the soluble variety is with difficulty reduced below *ca.* 1·5% even by prolonged dialysis. This ash was found to contain a high proportion of sulphate which amounted to about half that (*ca.* 1·25%) released on the hydrolysis of the polysaccharide itself, so that the presence of ethereal sulphate residues was apparent. Furthermore, treatment of the soluble laminarin with " Amberlite IR-100 (H) " to remove cations, dialysis, and titration with potassium hydroxide solution, both potentiometrically and to phenolphthalein, gave a product with an acid equivalent of *ca.* 8100 which would agree with the presence of *ca.* 1·2% of SO_4 in the polysaccharide. Autohydrolysis of this acid followed by examination on the paper chromatogram revealed the presence of fucose, although earlier experiments on the hydrolysis of soluble laminarin had seemed to show that glucose was the sole product of hydrolysis; the detection of fucose was facilitated by the fact that only a small quantity of free glucose was produced under the mild hydrolytic conditions employed. On re-examination of the hydrolysates of the soluble laminarin produced in the usual way, but with larger quantities on the paper chromatogram, it became clear that fucose was indeed produced on hydrolysis, a quantitative determination indicating the presence of 1·4%. The most obvious explanation is that the soluble laminarin examined contains a proportion (*ca.* 3·2%) of fucoidin (Percival and Ross, *J.*, 1950, 720). Attempts to lower the sulphate content by precipitation

methods failed but by the regeneration of the polysaccharide from the acetate the sulphate content fell to 0·83%. A similar fall was observed on electrodialysis, and when this process was repeated a product was obtained containing 0·38% of SO_4. Hydrolysis of the solution in the anode compartment and examination on the paper chromatogram showed the presence of more fucose than glucose, which is evidence that some separation had occurred. A determination of the reducing power of the electrodialysed polysaccharide by the hypoiodite method showed the value to be about double that recorded for the original material and to correspond to a chain length of *ca.* 57 glucose units. It might be concluded from this result that the fucoidin component, which is certainly difficult to remove, is associated in some way with the potential reducing group of the laminarin chain.

It is difficult to decide if it is the presence of the small amount of fucoidin which enhances the solubility of laminarin by acting as a protective colloid in accordance with Barry's suggestion (*loc. cit.*). Direct addition of isolated fucoidin to " normal " laminarin showed that although precipitation proceeded more slowly it was not inhibited, but it must be remembered that some modification of the fucoidin molecule may have taken place during the lengthy process of isolation (Percival and Ross, *loc. cit.*). Although a final answer to this question must, therefore, be deferred, it seems certain that there are no gross chemical differences between the two forms of laminarin examined.

Experimental.

Preparation of Soluble Laminarin.—Dried ground fronds of *Laminaria digitata* (500 g.) were extracted with dilute hydrochloric acid by counter-current extraction. A sample (50 g.) was stirred with dilute hydrochloric acid (0·088N.; 5 l.) for 24 hours and the weed residue removed by centrifugation. A second 50-g. sample was then added to the same solution and extracted in the same way. This process was repeated until the whole 500 g. had been extracted. To the extract was added lead acetate solution till precipitation was complete, followed by aqueous barium hydroxide to alkalinity to phenolphthalein. The combined precipitates were removed at the centrifuge, leaving a cloudy solution which was clarified by filtration through " Filter Cel." The solution (4350 c.c.) was then diluted with ethanol (25 l., to give 85%), and the laminarin which was precipitated was allowed to settle, washed by decantation with ethanol, and centrifuged off. After dialysis against running water for one week, the solution was evaporated to small bulk *in vacuo* and poured into ethanol (4 l.). The laminarin was filtered off, washed with alcohol and ether, and dried *in vacuo* over phosphoric oxide [yield, 38 g., containing 2·31% of ash and having $[\alpha]_D^{15}$ −12° (*c*, 4·37 in water)]. This specimen was used for the acetylations and methylations described below.

Hydrolysis.—Soluble laminarin by hydrolysis at 95° with N-sulphuric acid reached a constant rotation after 4½ hours and the solution after neutralisation, filtration, and evaporation to a syrup was analysed by paper chromatography which gave no indication of the presence of any reducing sugar other than glucose (Found: glucose, 95·3%).

Attempted Purification of Soluble Laminarin.—The presence of sulphur having been demonstrated by sodium fusion, determinations of the sulphate content after hydrolysis at 100° with hydrochloric acid (5%) for 3 hours gave SO_4 1·25%, SO_4 in ash 0·62%. Free sulphate was absent. Normal laminarin contained only a trace of sulphate.

An examination of hydrolysed soluble laminarin by filter-paper chromatography, using highly concentrated solutions, showed the presence of a small quantity of fucose. Determination (Hirst and Jones, *J.*, 1949, 1659) gave fucose 1·4%.

Since it was considered probable that fucoidin was present as an impurity the following experiments were carried out.

(1) Mercuric sulphate solution was added to a solution of soluble laminarin (5%), the small quantity of precipitate removed at the centrifuge, and the solution dialysed to remove inorganic salts, concentrated under diminished pressure, and precipitated in ethanol (Found: SO_4, 1·5%).

(2) To a solution of laminarin (5%) lead acetate solution (10 c.c.; saturated) was added, followed by barium hydroxide (saturated) until alkaline to phenolphthalein. After 18 hours the solution was filtered, and dialysed, and the laminarin recovered as before (Found: SO_4, 1·36%). In a control experiment with a synthetic mixture of normal laminarin (2 g.) and fucoidin (0·1 g.), 83% of the original sulphate content was removed by the above process.

(3) A solution of soluble laminarin (2 g. in 150 c.c. of water) was submitted to electrodialysis in a three-compartment cell for the use of which we are indebted to Dr. H. T. Macpherson, the cathode compartment being separated from the solution by a parchment membrane (8 × 12 cm.) and the anode compartment by a cloth membrane covered with gelatin. The electrodes were of platinum (3 × 2 cm.) and the centre compartment had a capacity of 250 c.c., and its contents were stirred mechanically throughout. The apparatus was operated at 300 v., the current rising to 600 milliamps. after 1 hour and falling to 120 milliamps. after 4 hours. The laminarin was isolated in the usual way (Found: SO_4, 0·82%). The contents of the cathode compartment were found to contain calcium ions. The contents of the anode compartment after evaporation, hydrolysis, and examination on the paper chromatogram gave spots on development with aniline oxalate corresponding to fucose with a smaller amount of glucose.

The product was submitted to a second electrodialysis (1 g. in 150 c.c. of water) in the same manner, the current rising to 200 milliamps. in 1·5 hours, and falling to 60 milliamps. in 5·5 hours. The isolated

laminarin on hydrolysis and examination on the paper chromatogram showed the presence of a trace of fucose only (Found : SO_4, 0·38%).

(4) Soluble laminarin acetate (2 g.) in chloroform (50 c.c.) was treated with sodium (0·1 g.) in methanol (10 c.c.) at 0° for 2 hours. The precipitate was then removed by filtration, and washed with chloroform, hot ethanol, and ether. The product had $[\alpha]_D^{18}$ −12° (*c*, 2·8 in water) (Found : SO_4, 0·83%).

Acetylation.—Samples of soluble and normal laminarin (3 g. each) were gelatinised by gentle warming with dry pyridine (30 c.c.), to give almost clear solutions to which was added acetic anhydride (9 c.c.). The solutions were kept in the dark for 3 days, during which slight precipitation occurred in both cases, and then poured into water (300 c.c.). After being kept overnight, the product was filtered off on a hardened filter paper, washed with water (2 l.) till free from acid, and dried in a vacuum-desiccator over phosphoric oxide. Yields and acetyl contents were 4·49 g. and 4·29 g., 44·0% and 44·9% for the soluble and normal forms respectively. $[\alpha]_D^{21}$ were −65° and −62° (*c*, 1·0 in chloroform).

Viscosity Measurements.—The viscosities of the two foregoing acetyl derivatives in *m*-cresol at 20° and in chloroform at 20° were determined by means of an Ostwald viscometer (see Table).

		Average time of flow in secs.			
	c.	Solution.	Solvent.	$\eta_{sp.}$	$\eta_{sp.}/c$.
In chloroform.					
Normal	0·0351	84·5	71	0·190	5·41
Soluble	0·0351	87·5	71	0·232	6·61
In m-*cresol.*					
Normal	0·0702	521	413	0·255	3·66
Soluble	0·0702	519	413	0·257	3·73

c represents the concn. of $C_6H_{10}O_5$ units per l.

The results obtained with chloroform solutions indicate a slight difference in the two samples but this is not confirmed by the results with *m*-cresol. In the latter case, by use of Staudinger's equation, $\eta_{sp.} = K_m Mc$ and taking K_m for the acetate as $6·3 \times 10^{-4}$ (the value for the corresponding cellulose derivatives, Staudinger and Reinecke, *Annalen*, 1938, **535**, 47) the apparent value for the molecular weights of both samples is found to be *ca.* 5800 but, since the true value for the constant is unknown, this figure only gives an indication of the order of magnitude of the molecular weights.

Methylation of Laminarin.—Laminarin (15 g.) was dissolved in sodium hydroxide solution (400 c.c.; 30%) at room temperature and the solution methylated by the gradual addition during 5 hours, with stirring, of methyl sulphate (140 c.c.). Stirring was continued overnight, the reaction mixture was neutralised with sulphuric acid and evaporated almost to dryness (40°/15 mm.), and the solution methylated as before. Dialysis in Cellophane bags against running water removed soluble sulphates, and the solution was then evaporated to small bulk. Two further methylations were carried out in the same manner. After dialysis and evaporation to dryness, a sample of the product was dissolved in chloroform and dried (Na_2SO_4), and the chloroform evaporated off to small bulk. The methylated compound was then precipitated with light petroleum (b. p. 60—80°), filtered off, and dried *in vacuo* (Found : OMe, 41·0%; ash, nil). The bulk of the material was then suspended in acetone (100 c.c.), and sodium hydroxide solution (200 c.c.; 30%) added. Methyl sulphate (70 c.c.) was then added with stirring during 4 hours, and stirring continued overnight. When the mixture was warmed to remove acetone, the methylated compound coagulated and was filtered off through muslin and remethylated as before. The coagulated product of the second methylation was dissolved in chloroform, and the residual liquor extracted with chloroform. The combined chloroform solutions were dried (Na_2SO_4) and evaporated to 50 c.c., and the methylated lamina in precipitated with light petroleum (b. p. 30—80°; 4 l.), separated off, and dried (Found : OMe, 43·3%; ash, 0·49%). In an attempt to raise the methoxyl content still further, two more methylations in acetone as described were carried out, yielding finally 9·8 g. of methylated laminarin (OMe, 44·1; ash, 0·31%).

Fractionation of Methyl Laminarin.—By addition of increasing amounts of light petroleum to a chloroform solution of methyl laminarin, various fractions were obtained but, as no analytical differences could be observed, these were later recombined.

Qualitative Paper-chromatographic Analysis of Methyl Laminarin.—Methyl laminarin (50 mg.) was treated with methanolic hydrogen chloride (1 c.c.; 4%) in a sealed tube at 95° for 7 hours. The tube was then opened and hydrolysis continued by heating with additional aqueous hydrochloric acid (5 c.c.; 4%) for 7 hours at 95° under reflux. The solution was neutralised with silver carbonate and treated with hydrogen sulphide to remove excess of silver, and the filtered solution finally treated with Amberlite ion-exchange resins to remove salts. After evaporation to small bulk, the solution was used for qualitative paper-chromatographic analysis with the following results. The paper strips on development with aniline oxalate solution indicated (1) tetramethyl glucopyranose, R_G, 1·00, weak, (2) 2 : 4 : 6-trimethyl glucose, R_G, 0·81, very strong, (3) 2 : 6-dimethyl glucose R_G, 0·54, weak pink spot, and (4) 4 : 6-dimethyl glucose, R_G, 0·49, very weak brown spot.

Separation of Methylated Glucose.—Methylated laminarin (2·71 g.) was treated in a sealed tube with methanolic hydrogen chloride (60 c.c.; 4%) at 100° for 7 hours. The acid was then neutralised with silver carbonate, the silver chloride filtered off, and the solution evaporated to dryness (40°/15 mm.). Sulphuric acid solution (400 c.c.; N.) was added to the residue, and the hydrolysis continued under reflux at 95° for 10 hours. After neutralisation with barium carbonate, filtration, and washing of the precipitate, the combined solutions were evaporated to a syrup (40°/15 mm.). The syrup was redissolved

and filtered through " Filter Cel " to remove trace of barium salts, and the syrup (2·89 g.) recovered by evaporation.

The syrup which partly crystallised was then separated on a column of powdered cellulose by the method of Chanda *et al.* (*J.*, 1950, 1289), using as solvent a mixture of 70% light petroleum (b. p. 100—120°) and 30% butanol saturated with water. The collected fractions were dissolved in water, warmed with charcoal, and filtered through " Filter Cel," and the solution and washings were evaporated to syrups which were dissolved in acetone, refiltered, and evaporated, and the syrup dried over phosphoric oxide *in vacuo*.

By elution with solvent, fraction (I) 0·756 g., and (II) 1·747 g., and by elution with water fraction (III) 0·180 g. were obtained. The fractions were shown by qualitative paper-chromatography to comprise (I) tetramethyl glucopyranose, (II) trimethyl glucose, (III) dimethyl glucoses (2) as far as free reducing sugars were concerned. Hypoiodite estimations of the free sugars on fractions (I) and (III) indicated that neither consisted solely of free sugars, fraction (I) containing 19·2% of free reducing sugar as tetramethyl glucose or 5·04% on the original syrup, and fraction (III) 65·8% as dimethyl glucose or 4·10% on original syrup.

Fraction (I) (0·747) was rehydrolysed with hydrochloric acid (2N.) for 5 hours at 95°, neutralised with silver carbonate, treated with hydrogen sulphide, filtered, and evaporated to a syrup (0·718 g.). This syrup was chromatographed as before, yielding two fractions (I*a*) and (II*a*) consisting of tetramethyl glucopyranose (0·242 g.) and trimethyl glucose (0·445 g.) respectively, showing that incomplete hydrolysis had taken place in the first experiment. Hypoiodite estimation showed that the tetramethyl glucose fraction contained 61·6% of free sugar, equivalent to 5·15% on the original hydrolysed syrup, which corresponds to a chain length of 20—21 glucose units in the polysaccharide.

These results may be summarised thus: tetramethyl glucopyranose 5·15%, trimethyl glucose (allowing for glucoside in fraction I) 80·2%, dimethyl glucose 4·10%, unaccounted portion of dimethyl fraction 2·10%, total recovery 92%.

Purification of Tetramethyl Glucose (*Fraction I*a).—This fraction (0·242 g.) was recrystallised from dry light petroleum (b. p. 40—60°), yielding 0·113 g. of purer crystalline material which was recrystallised, giving crystals (0·071 g.), m. p. 82—86°, and $[\alpha]_D^{15}$ +82° (equilibrium) (*c*, 0·71 in water) representing 96% purity. A second crop of crystals was obtained on partial evaporation of the solvent (0·014 g.). The m. p. of neither sample was depressed on admixture with authentic tetramethyl glucopyranose. The residual tetramethyl glucose was determined by hypoiodite oxidation on the combined mother-liquors, showing a further 0·060 g. to be present. The total amount of tetramethyl glucopyranose was, therefore, 0·145 g. or 5·02% on the original hydrolysate which is in good agreement with the 5·15% obtained in the original hypoiodite determination.

Partial Demethylation of 2 : 4 : 6-*Trimethyl Glucose.*—Pure 2 : 4 : 6-trimethyl glucose (0·257 g.) obtained by recrystallisation from fraction (II) above was treated with methanolic hydrogen chloride (6 c.c.; 4%) in a sealed tube at 95° for 7 hours, then neutralised with silver carbonate, the solution filtered, and the precipitate washed with dry methanol. The filtrate and washings were evaporated to a syrup (40°/15 mm.), and hydrolysis continued at 95° with sulphuric acid (2 c.c.; N.) for 10 hours. After neutralisation, filtration, and evaporation a syrup was obtained which showed on a qualitative paper-chromatogram, in addition to trimethyl glucose, a small quantity of dimethyl glucose. Quantitative determination by the same method gave dimethyl glucoses 2·86%. By use of larger amounts of syrup on a qualitative chromatogram, two dimethyl glucoses were observed having the same R_G values as those obtained from the methyl laminarin hydrolysate and in approximately the same relative amounts. Unfortunately the R_G values of the sugars occur too close together for separate quantitative determination, but these results indicate the origin of a large proportion of the dimethyl sugars separated on the cellulose column.

The Reducing Power of Soluble Laminarin.—(1) *Oxidation with alkaline hypoiodite.* To specimens of normal and soluble laminarin (0·3 g. each), iodine solution (10 c.c.; 0·1N.) and sodium hydroxide (15 c.c.; 0·1N.) were added. After 1 hour the solution was acidified and the excess of iodine determined by titration. The consumptions of iodine corresponded to one aldehyde group in 45 glucose units for normal laminarin and in 112 glucose units for soluble laminarin. Later experiments, the results of which are given in the Table below, indicated that warming of the laminarin with sodium hydroxide

Treatment.	Apparent no. of glucose units/reducing group.
Soluble laminarin.	
(1) Direct treatment with I–NaOH	112
(2) Warmed to 40° (1 min.) in NaOH (15 c.c.; 0·1N.), cooled, + iodine	87
(3) Electrodialysed product (ash, 0·38%); as (1)	57
Normal laminarin.	
(4) As (1)	45
(5) As (2)	32
(6) Warmed to dissolve in water (10 c.c.), cooled, +NaOH (5 c.c.; 6N.), + iodine	45
(7) Warmed to 40° (1 min.) in water (7·5 c.c.), cooled, +NaOH (7·5 c.c.; 0·2N.), + iodine	43
(8) As (6), but left for 3 days before addition of iodine	29
(9) Warmed to 40° (5 mins.) in NaOH (15 c.c.; 0·1N.), cooled, + iodine	17
(10) As (4), but with 2N-NaOH	29
(11) Warmed to 65° (30 mins.) in NaOH (15 c.c.; 2N.), cooled, + iodine	8

before the addition of the iodine caused an apparent increase in the reducing power and therefore a reduction of the apparent chain length. In the case of normal laminarin, on which most of the determinations were made owing to its availability, the apparent reducing power was increased to the equivalent of one reducing group in 8 glucose units by treatment for ½ hour at 65° with 2N-sodium hydroxide.

(2) *Colorimetric method.* As in Meyer's method (*Helv. Chim. Acta*, 1948, **31**, 103), a solution of the polysaccharide (2 c.c.; 0·5%) was heated with water (1 c.c.), 3 : 5-dinitrosalicylic acid solution (1 c.c.; 1·5%), and sodium hydroxide (1 c.c.; 6N.) at 65° for 30 minutes, the solution being then cooled and diluted to 25 c.c. The colour was then compared with a blank solution in a Spekker absorptiometer (4-cm. cell; filter 604). The readings were then compared with a graph obtained by treating laminaribiose in the same way at various concentrations. The readings thus obtained gave values for the chain lengths of soluble and normal laminarins of 27 and 13 $C_6H_{10}O_5$ units respectively. However, in view of the results obtained above for the effect of heating the polysaccharide with alkali, the interpretation of these results is open to doubt.

Oxidation of Laminarin with Potassium Periodate.—(a) *Determination of formic acid liberated.* Samples (0·5 g.) of soluble and normal laminarin were shaken in the dark with sodium metaperiodate (15 c.c.; 0·3M.), potassium chloride (5 g.), and water (105 c.c.) for 14 days, a blank experiment being run at the same time. At intervals samples (10 c.c.) were withdrawn and titrated to methyl-red with 0·01N-sodium hydroxide after the addition of ethylene glycol. For the normal laminarin it was necessary to separate the insoluble material at the centrifuge. After application of the necessary corrections (Halsall, Hirst, and Jones, *J.*, 1947, 1399, 1427) the following results (in c.c. of 0·01N-NaOH) were obtained: Soluble laminarin, 3·71 c.c. (3 days); 4·42 c.c. (7 days); 4·66 c.c. (14 days). Normal laminarin, 2·38 c.c. (3 days); 3·65 c.c. (7 days); 3·70 c.c. (14 days). The values after 7 days correspond to the release of 1 mol. of formic acid from 5·6 and 6·7 $C_6H_{10}O_5$ units for soluble and normal laminarin respectively.

(b) *Formaldehyde production* [With W. E. A. Mitchell]. Soluble laminarin (0·5 g.), potassium periodate (1 g.), and water (20 c.c.) were shaken in the dark for 4 days. The contents were then separated at the centrifuge, a sample (15 c.c.) of the liquid was removed and acidified with dilute hydrochloric acid (2N.), and the iodine liberated removed by the addition of sodium arsenite solution (1·4N.). The solution was then buffered with acetate buffer to pH 4·6, dimedone solution [160 mg. in ethanol (2 c.c.)] added, and the mixture heated on the steam-bath for 20 minutes. After being set aside overnight the dimedone–formaldehyde compound was removed on a sintered filter-stick (porosity 4) and dried to constant weight in a drying block. The yield was 0·0280 g., and the m. p. 185—186° corresponding to the liberation of 1 mol. of formaldehyde from 30 $C_6H_{10}O_5$ units.

Treatment of Laminarin with "Amberlite 1*R*-100 (*H*)."—Samples of soluble laminarin (ash, 2·0%) and normal laminarin (ash, 0·28%) were dialysed against distilled water for 3 days to remove simple salts, and the polysaccharides recovered by concentration and the addition of ethanol. Ash (1·81%) was still present in the soluble laminarin, of which 0·23% only was due to the presence of siliceous matter as determined by the loss in weight on treatment with sulphuric and hydrofluoric acids. The purified specimens of soluble laminarin (0·326 g.) and normal laminarin (0·919 g.) in water (10 c.c.) were shaken with "Amberlite 1R-100 (H)" resin overnight. After dialysis against distilled water for 2 days to remove any inorganic acid, the solution which was still acid was filtered, the resin was washed, and the filtrate and washings were titrated against potassium hydroxide (0·01N.) potentiometrically in the presence of phenolphthalein using antimony and calomel/saturated potassium chloride electrodes. The end-points to phenolphthalein were noted during the course of the titrations. The results are given in the Table below. In the case of soluble laminarin the solution after titration was dialysed to remove

Titres with 0·01N-KOH *and corresponding potentiometric readings for the various acids.*

Soluble laminarin (0·326 g.).				Normal laminarin (0·919 g.).			
KOH, c.c.	mv.	KOH, c.c.	mv.	KOH, c.c.	mv.	KOH, c.c.	mv.
—	191	3·53	262	—	198	3·00	264
0·50	191	4·01	300	0·31	198	3·50	304
1·00	194	4·63	370	0·81	202	4·00	346
1·50	198	4·87 *	404	1·20	207	4·51 *	388
2·00	204	5·40	455	1·50	212	5·00	454
2·50	212	5·94	485	1·91	220	5·50	486
3·00	226	7·05	570	2·49	238	6·00	502
						6·50	514

* End-point to phenolphthalein.

excess of alkali, then evaporated (40°/15 mm.), and the laminarin precipitated in alcohol. The ash content of the product was 1·99%. A blank titration after shaking of the resin with water overnight and dialysis gave a titre of 0·90 c.c. of potassium hydroxide (0·01N.).

Graphs were drawn of titre against millivolts. From the curves and the phenolphthalein end-points, the alkali used after allowance for the blank is equivalent in the case of soluble laminarin to 1 equivalent of acid in 8100 g., and for normal laminarin in 25,000. These figures correspond to SO_4 1·2% and 0·4% respectively, the acidity being assumed to be due to an ethereal sulphuric acid residue.

Autohydrolysis.—A solution of soluble laminarin, after overnight shaking with "Amberlite 1R-100 (H)" and removal of the resin, was heated at 95° for 1·5 hours. Barium carbonate was added to the hot solution, which after filtration was poured into ethanol. Filtration, evaporation, and examination on the filter-paper chromatogram revealed the presence of fucose as the principal sugar component together with a smaller quantity of glucose.

Uronic Acid in Laminarin.—By McCready, Swenson, and Maclay's method (*loc. cit.*) uronic acid determinations on both types of laminarin gave results of 0·84% for soluble and 0·70% for normal laminarin, but these figures are probably within the experimental error of the determination.

Molecular Weight by Barger's Method.—The micro-molecular weight method of Barger (*J.*, 1904, 286) as modified for high polymers (Caesar, Gruenhut, and Cushing, *J. Amer. Chem. Soc.*, 1947, **69**, 617) was applied to methylated soluble laminarin as follows. Droplets of a 1·13% solution of this derivative in chloroform were compared in capillary tubes, with solutions of sucrose octa-acetate ($2·5 \times 10^{-3}$M.), using a travelling microscope reading to 0·02 mm. The isopiestic condition was found to be between 3×10^{-3} and 4×10^{-3}M-sucrose octa-acetate solution, from which the molecular weight appears to lie between 3800 and 2800, corresponding to a chain length of 14—18 $C_6H_{10}O_5$ units.

Effect of Added Fucoidin on the Precipitation of Laminarin.—Known amounts (2—5 g.) of normal laminarin were dissolved in hot water (100 c.c.) and allowed to cool to room temperature. Sufficient fucoidin to make up 2·5% of the total was added to two of the solutions, together with sufficient hydrochloric acid to simulate the conditions of extraction. The deposited laminarin was removed after standing. Precipitation: Normal laminarin, 1 day 33; 2 days 66%. Laminarin + 2·5% fucoidin, 1 day 12; 2 days 61%.

X-*Ray Powder Photographs of Laminarin.*—Through the kindess of Dr. C. A. Beevers specimens of laminarin were examined, using a copper target and 1·5 hours' exposure (25 mA.; 50 kv.). The photographs given by specimens of normal and soluble laminarin were identical. They both showed a vague halo rather sharper on its low-order side than on its high-order side, corresponding to a spacing of 2·2 A.

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157. *Acylation Reactions catalysed by Strong Acids. Part V. Mixtures of Zinc Chloride and Acetyl Chloride or Acetic Anhydride as Sources of Acetylium Ions.*

By H. BURTON and P. F. G. PRAILL.

Mixtures of zinc chloride and an excess of acetyl chloride or acetic anhydride are good sources of acetylium ions and will convert anisole into *p*-methoxyacetophenone in high yields. The catalytic activity of the salt for the reaction between anisole and acetyl chloride is considerable.

THE electronic configuration of zinc chloride is such that, when it is used as a catalyst for the Friedel–Crafts reaction, there could be produced from an acid chloride or acid anhydride twice as many acylium ions (acyl cations) per molecule of salt as when aluminium chloride is employed. Completion of the outer octet of electrons would necessitate the following reactions:

$$ZnCl_2 + 2R{\cdot}COCl \longrightarrow (R{\cdot}CO)_2^{++}[ZnCl_4]^{--}$$
$$ZnCl_2 + 2(R{\cdot}CO)_2O \longrightarrow (R{\cdot}CO)_2^{++}[ZnCl_2(O{\cdot}COR)_2]^{--}$$

If the production of acylium ions was the sole factor in determining the success of the Friedel–Crafts reaction, then clearly zinc chloride should be a far more efficient catalyst than aluminium chloride, which can give rise to only one acyl cation per molecule. It is well known however that zinc chloride is generally considered to be a not very efficient catalyst. We would point out however that mixtures of zinc chloride and acetic anhydride–acetic acid have often proved useful (see Johnson, "Organic Reactions," Vol. II, 1944, p. 114) for the intramolecular Friedel–Crafts reaction leading to cyclic ketones. It seems probable in these cases that the carboxylic acid and the acetylium ion (or its equivalent) react as follows:

$$R{\cdot}CO_2H + Ac^+ \rightleftharpoons R{\cdot}CO{\cdot}O^+H{\cdot}CO{\cdot}CH_3 \rightleftharpoons R{\cdot}CO^+ + AcOH$$

and that cyclisation depends on the loss of a proton from the $R{\cdot}CO^+$ ion which must, of necessity, be suitably constituted if the overall reaction is to take place.

We now show that zinc chloride (1 mol.) with an excess of acetic anhydride will rapidly convert, under relatively mild conditions, more than 1 mol. of anisole into *p*-methoxyacetophenone. Thus with a molecular ratio of zinc chloride, anisole, and acetic anhydride of 1 : 2 : 4

there is an extremely rapid production of 1·2 mols. of isolable ketone.* With a ratio of 1 : 3 : 4 in the presence of nitromethane we isolated as much as 1·4 mols. of *p*-methoxyacetophenone after the same time interval, presumably because of the increased rate of reaction. We conclude that these results prove that the above reaction between acetic anhydride and zinc chloride does in fact occur. During these experiments there is no evolution of hydrogen chloride or acetyl chloride and it is thus clear that the reaction with anisole proceeds as follows :

$$Ac_2^{++}[ZnCl_2(OAc)_2]^{--} + 2PhOMe \longrightarrow 2OMe{\cdot}C_6H_4{\cdot}COMe + H_2^{++}[ZnCl_2(OAc)_2]^{--}$$
$$H_2^{++}[ZnCl_2(OAc)_2]^{--} \longrightarrow 2AcOH + ZnCl_2$$

We have also shown that mixtures of zinc chloride and acetic acid have no action on anisole : furthermore, acetic anhydride and anisole alone do not give any ketone when an equimolecular mixture is boiled for several hours.

It will be apparent from the above scheme that, provided no side reactions involving the zinc chloride occurred, the process should be a strictly catalytic one. Actually, the *p*-methoxyacetophenone formed reacts with acetic anhydride and zinc chloride to give a yellow crystalline compound (containing zinc), which is highly fluorescent in alcoholic solution and is undoubtedly a pyrylium salt of the type described by Dilthey (*J. pr. Chem.*, 1916, [ii], **94**, 75). We have mentioned previously (*J.*, 1950, 1203) the formation of an analogous compound in experiments with anisole, acetic anhydride, and perchloric acid.

The formation of the fluorescent salt clearly occurs at a much slower rate than the acetylation of anisole, and accordingly we have carried out a series of experiments using an equimolecular mixture of anisole and acetyl chloride to which was added very small amounts of some typical Friedel–Crafts catalysts, in an attempt to decide whether a strictly catalytic effect could, in fact, be observed. We first showed that *p*-methoxyacetophenone, acetyl chloride, and zinc chloride gave, under similar conditions, the same type of yellow fluorescent solid. Incidentally we found that such mixtures gave an intense deep blue colour as soon as the mixture was warmed.

It has however been reported by Dermer, Wilson, Johnson, and Dermer (*J. Amer. Chem. Soc.*, 1941, **63**, 2881, footnote) that anisole and acetyl chloride react in the absence of any catalyst to give an approximately 30% yield of *p*-methoxyacetophenone : no experimental details were given. We have therefore carried out all our experiments with AnalaR acetyl chloride and purified anisole which when refluxed for 4—8 hours in equimolecular proportions gave only traces (maximum yield, 0·15% of anisole used) of the ketone. Our experiments clearly indicate that these authors must have been using acetyl chloride which was probably contaminated with a metallic chloride : we shall refer to this point at a later stage.

Our experiments with traces of three typical metal chlorides, namely, aluminium, ferric, and zinc, indicate clearly that for added small amounts (0·075% of the weight of acetyl chloride) and a reaction period of 4 hours the yield of *p*-methoxyacetophenone is increased out of all proportion to the amount of catalyst used. The amounts of ketone actually isolated, as such or as the 2 : 4-dinitrophenylhydrazone, were of the order of 2·2% for aluminium and ferric chlorides and 7·2% for zinc chloride. The result with zinc chloride was not altogether unexpected since it seemed that the zinc chloride was inactivated at a much slower rate than either aluminium or ferric chloride. We decided therefore to investigate the activity of zinc chloride in more detail. An increase in the reaction time from 4 to 7 hours for the same amount of catalyst resulted in an improved yield (at least 8·4%), and an increase in the amount of the salt (to 0·19%) resulted in a further increase in the yield of ketone to at least 11·7% after 7 hours. The last result is more illuminating if expressed in the following way : addition of approximately 0·00025 g.-mol. of zinc chloride (technical or its equivalent of pure or AnalaR anhydrous zinc acetate, which must be converted into the chloride under the experimental conditions) to a mixture of 0·2 g.-mol. each of anisole and acetyl chloride results in the production after 7 hours' refluxing of no less than 0·0233 g.-mol. of *p*-methoxyacetophenone. The molecular ratio of ketone isolated to catalyst used is thus at least 93 : 1.

In this series of experiments with anisole we observed some striking colour changes : a purple colour of varying intensity develops with the use of the metal chlorides and in the case of zinc chloride becomes progressively more brown. At the same time orange crystalline material separates slowly during the reaction and this is undoubtedly a pyrylium zincichloride since it resembles, and is probably identical with, that produced in the zinc chloride–acetic anhydride experiments. It is clear that the zinc chloride is slowly inactivated in this way.

* This method is recommended as a rapid, simple, and cheap method of preparation of *p*-methoxyacetophenone.

We have referred above to the reported production (Dermer *et al.*, *loc. cit.*) of a large amount of *p*-methoxyacetophenone from anisole and acetyl chloride alone. We cannot substantiate this claim and our suggestion that their acetyl chloride was probably contaminated with a metallic chloride was prompted by our own results: it appears to us that zinc chloride was the most probable impurity. We have shown incidentally that the impurity could not have been pyridine, thionyl chloride, sulphur monochloride, or phosphoryl chloride since no ketone could be isolated in the first three cases and only about 0·5% in the last case. We attach some importance to the probable, doubtful quality of the acetyl chloride used by Dermer *et al.* (*loc. cit.*) in their work, since their results on the efficiency of a series of metallic chlorides, admittedly towards toluene and the acetyl chloride, is now quoted in the literature (see, for example, Sidgwick, "Chemical Elements and their Compounds," Oxford, 1950, p. 437). We feel that this series should be accepted with some reserve since it is probable that all the metallic chlorides used had an impurity added to them in the acetyl chloride.

It is noteworthy that, in all the experiments using zinc chloride as the catalyst, the salt goes into solution in the reaction mixture. Salts of similar electronic configuration, for example, mercuric chloride, cadmium chloride, calcium chloride, have not been studied very extensively. Dermer *et al.* (*loc. cit.*) state that these salts are inactive for toluene and we have shown that cadmium and calcium chlorides were both insoluble in acetic anhydride–anisole mixtures and hence inactive. Mercuric chloride however did dissolve in a boiling mixture of the reagents and an appreciable amount of *p*-methoxyacetophenone was produced: in addition, much crystalline material which was probably mercurated substance, but which was not investigated, was also formed.

We conclude that our experiments involving the use of zinc chloride, with either acetyl chloride or acetic anhydride, prove conclusively that acetylium ions are formed; these are sufficiently reactive, as we have shown previously (*J.*, 1950, 1203, 2034), to acetylate the highly activated anisole molecule. It would appear from our results that zinc chloride is a more efficient catalyst than aluminium chloride for the *C*-acetylation of anisole. We attribute this higher efficiency entirely to the slower rate of inactivation of the salt. We wish to make it quite clear that we do not suggest that zinc chloride is, in general, a more efficient catalyst than is aluminium chloride. On the contrary, we now show that for benzene and acetic anhydride the use of zinc chloride gives, even in the presence of nitromethane, only a trace of acetophenone, whereas aluminium chloride, benzene, and acetic anhydride are known (Adams, *J. Amer. Chem. Soc.*, 1924, **46**, 1889) to afford the ketone rapidly and in high yield.

We have pointed out (p. 727) that in our experiments with anisole, acetic anhydride, and zinc chloride there was no evolution of either hydrogen chloride or acetyl chloride. We conclude from this that there is no tendency, in this particular system,* for either of the following modes of decomposition of the complex salts to occur:

$$R_2^{++}[ZnCl_2(OAc)_2]^{--} \longrightarrow RCl + R^+[ZnCl(OAc)_2]^-$$
$$\downarrow$$
$$2RCl + Zn(OAc)_2 \qquad (R = H \text{ or Ac.})$$

The result for R = Ac is in marked contrast to the use of aluminium chloride (Adams, *loc. cit.*), which clearly reacts with acetic anhydride and an aromatic compound (ArH) as follows:

$$AlCl_3 + Ac_2O \longrightarrow Ac^+[AlCl_3{\cdot}OAc]^-$$
$$ArH + Ac^+[AlCl_3{\cdot}OAc]^- \longrightarrow Ar{\cdot}COMe + H^+[AlCl_3{\cdot}OAc]^-$$
$$H^+[AlCl_3{\cdot}OAc]^- \longrightarrow HCl + AlCl_2{\cdot}OAc$$

We have shown that acetoxyaluminium dichloride, $AlCl_2{\cdot}OAc$, which we believe to be formed (in solution) from aluminium chloride (1 mol.) and acetic anhydride (1 mol.) in nitrobenzene with subsequent removal of acetyl chloride is, for all practical purposes, inactive as a catalyst for the reaction between anisole and acetic anhydride.

Experimental.

Materials.—Zinc chloride was a commercial preparation of 95% purity. Zinc acetate (pure and AnalaR) was dried to constant weight at 110° before use. Acetyl chloride and acetic anhydride were AnalaR reagents.

p-*Methoxyacetophenone from Anisole, Acetic Anhydride, and Zinc Chloride.*—(*a*) A mixture of zinc chloride (0·2 g.-mol.), acetic anhydride (0·8 g.-mol.), and anisole (0·4 g.-mol.) was well shaken for

* With benzene, acetic anhydride, and zinc chloride in nitromethane there is some evolution of hydrogen chloride; in the absence of nitromethane no evolution occurred.

5—7 minutes during which the internal temperature rose to 50—60° and dissolution of the zinc chloride occurred. The solution was then heated on the steam-bath to 80°, the total reaction time being 12 minutes. The mixture was then cooled rapidly to 25—30° and poured on crushed ice (*ca.* 300 g.). Addition of ether caused the separation of a variable amount of an orange solid (*A*); this was filtered off from the ethereal solution and washed with ether. The filtered ethereal extract of the oily reaction product was washed successively with water, dilute sodium carbonate solution, an excess of dilute sodium hydroxide solution (which appeared to remove a little phenolic product), and finally with water. The dried (Na_2SO_4) extract was then evaporated and the residue fractionated at about 4 mm., whereby a good separation of *p*-methoxyacetophenone (0·24 g.-mol.), b. p. 110—115°/3·8—4 mm., from a little unchanged anisole was obtained. The ketone solidified, on cooling, to a pale yellow mass of crystals, m. p. 34—37°, identified as its 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 223°.

Solutions of the solid (*A*) in alcohol or acetone showed an intense green fluorescence.

(*b*) A mixture of zinc chloride (0·1 g.-mol.), acetic anhydride (0·4 g.-mol.), anisole (0·3 g.-mol.), and nitromethane (147 g.), under conditions identical with those described in (*a*), gave 0·14 g.-mol. of *p*-methoxyacetophenone.

With zinc chloride (0·05 g.-mol.), acetic anhydride (0·1 g.-mol.), anisole (0·1 g.-mol.), and nitromethane (42 g.) under the same conditions, 0·056 g.-mol. of *p*-methoxyacetophenone was isolated.

In all the experiments a dark residue (1·1—1·9 g.) remained in the distillation flask; this contained an appreciable amount of the ketone which was identified as its 2 : 4-dinitrophenylhydrazone. There was no evolution of hydrogen chloride or other volatile product in any of the experiments. A longer reaction time or the use of a higher temperature gave increasing amounts of the solid (*A*) and a diminished yield of ketone.

p-*Methoxyacetophenone from Anisole, Acetic Anhydride, and Mercuric Chloride.*—In this case it was found necessary to use a much larger amount of acetic anhydride to obtain complete dissolution. A mixture of mercuric chloride (0·2 g.-mol.), anisole (0·4 g.-mol.), and acetic anhydride (1·6 g.-mols.) was boiled under reflux until complete dissolution occurred. The orange-yellow crystalline material which separated on cooling was filtered off and the filtrate added to crushed ice. Extraction of the oily reaction product with ether followed by repeated washing with water and finally with dilute sodium hydroxide solution gave (as above) 0·11 g.-mol. of *p*-methoxyacetophenone. The crystalline material was not further investigated.

Reaction of Anisole and Acetyl Chloride in Absence and Presence of Small Amounts of Zinc Chloride and Other Substances.—In the preliminary experiments, a mixture of acetyl chloride (0·1 g.-mol.), anisole (0·1 g.-mol.), and a small crystal of the solid or a drop of the liquid under investigation was boiled under reflux with a calcium chloride guard-tube for 4—8 hours. Unchanged reagents were removed by distillation at atmospheric pressure using a small column, and the residue treated with an alcoholic solution of 2 : 4-dinitrophenylhydrazine sulphate. The yield of ketone was then calculated from the weight of *p*-methoxyacetophenone 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 223°. Acetyl chloride and anisole alone gave a trace of ketone after 4 hours and 0·15% after 8 hours. No ketone could be detected when using sulphur and thionyl chlorides for 4 hours or pyridine for 6 hours. With phosphoryl chloride, ferric chloride, and aluminium chloride for 4 hours the yields of ketone were 0·54, 2·2, and 2·3%, respectively; under the same conditions zinc chloride gave 7·2% of the ketone which was isolated as such by distillation in a vacuum; it had b. p. 125°/5·5 mm., m. p. 39°.

In subsequent experiments with zinc chloride and zinc acetate, 0·2 g.-mol. each of acetyl chloride and anisole were used and the mixture was boiled for 7 hours. It was noticed that the zinc salt did not dissolve in the acetyl chloride but rapid dissolution occurred when the anisole was added and a purple colour developed. A fairly rapid evolution of hydrogen chloride occurred during the initial stage of the reaction and, after about 1½ hours, bright orange crystals began to separate and the colour of the reaction mixture became browner. When the reaction mixture had cooled the crystals (*B*) were filtered off and washed with ether. The *p*-methoxyacetophenone was isolated by distillation. The yields of ketone and (*B*), when 32 mg. of zinc chloride were used, were 3·5 g. (11·7%) and 83 mg., respectively. With 39 mg. of zinc acetate the yields were 11·3% and 88 mg., respectively, and with 29 mg. of zinc acetate the yield of ketone was 9·7%.

The solid (*B*) had m. p. 258—260° (decomp.) and on ignition gave a residue of zinc oxide. It was sparingly soluble in alcohol; solutions showed an intense green fluorescence.

Reaction between Benzene and Acetic Anhydride–Zinc Chloride.—(*a*) A mixture of benzene (0·4 g.-mol.), acetic anhydride (0·8 g.-mol.), and zinc chloride (0·2 g.-mol.) was heated on a boiling water-bath with occasional shaking until all the zinc chloride had dissolved (*ca.* 5 minutes). After a further 30 minutes, during which no evolution of hydrogen chloride occurred, the dark solution (initially deep red) was cooled rapidly and poured on crushed ice. The aqueous phase was extracted with ether and the combined benzene–ether extracts were washed successively with water, dilute sodium carbonate solution, 2N-sodium hydroxide (whereby most of the colour was removed), and water. The small amount of residue from the dried (Na_2SO_4) extract gave 60 mg. of impure acetophenone 2 : 4-dinitrophenylhydrazone.

(*b*) A mixture of benzene (0·1 g.-mol.), acetic anhydride (0·2 g.-mol.), zinc chloride (0·05 g.-mol.), and nitromethane (56·4 g.) was similarly heated until all the zinc chloride had dissolved (*ca.* 30 minutes); a very slow evolution of hydrogen chloride occurred. After a further 30 minutes the mixture was treated as described in (*a*). The small residue from the dried extract gave a trace of impure acetophenone 2 : 4-dinitrophenylhydrazone.

Acetoxyaluminium Dichloride.—Acetic anhydride (0·1 g.-mol.) was added dropwise to a solution of aluminium chloride (0·1 g.-mol.) in nitrobenzene (53·6 g.), whereby a white translucent paste separated

and the mixture became warm. The mixture was then heated (oil-bath) gradually during 1—1½ hours to 170°, the volatile product being allowed to distil. The mixture was then cooled and reheated to 110° in a vacuum (water-pump) during 30 minutes. The resulting dark brown solution was mixed with anisole (0·1 g.-mol.) and acetic anhydride (0·2 g.-mol.) and heated (bath) at 110—120° for 2 hours. After cooling, the mixture was poured into 2N-hydrochloric acid (150—200 c.c.), then filtered, and the filtrate extracted with ether. The ethereal extract was washed twice with 2N-sodium hydroxide and then with water. Fractionation of the residue from the dried (Na_2SO_4) extract gave anisole (0·065 g.-mol.) and a small amount of *p*-methoxyacetophenone identified as the 2 : 4-dinitrophenylhydrazone (yield, 0·4 g.).

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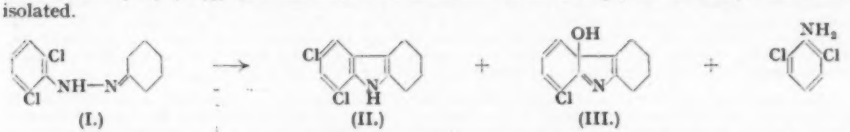
158. *The Fischer Indole Synthesis. Part V. The Cyclisation of Some* cyclo*Hexanone* o*-Substituted Hydrazones.*

By C. S. BARNES, K. H. PAUSACKER, and (in part) W. E. BADCOCK.

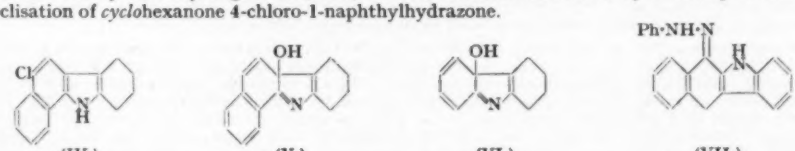
Di-*o*-substituted hydrazones of *cyclo*hexanone yield both 1 : 2 : 3 : 4-tetrahydrocarbazoles (by rearrangement) and 1 : 2 : 3 : 4-tetrahydro*iso*carbazoles. *cyclo*Hexanone *o*-bromophenylhydrazone yields novel products, and camphenilone phenylhydrazone is converted into a compound which is normally postulated as a hypothetical intermediate in the Fischer indole synthesis.

CARLIN AND FISHER (*J. Amer. Chem. Soc.*, 1948, **70**, 3421) have found that *cyclo*hexanone 2 : 6-dichlorophenylhydrazone (I) is converted, in very small yield (0·3%), into 6 : 8-dichloro-1 : 2 : 3 : 4-tetrahydrocarbazole (II), by use of zinc chloride in nitrobenzene as the catalyst. This cyclisation has been repeated, with aqueous sulphuric acid as the catalyst, and in addition to (II) (24%) both 2 : 6-dichloroaniline (5%) and 8-chloro-1 : 2 : 3 : 4-tetrahydro-12-hydroxy-*iso*carbazole (III) (37%) (cf. Barnes, Pausacker, and Schubert, *J.*, 1949, 1381) have been isolated.



(I.) (II.) (III.)

When *cyclo*hexanone 2 : 6-dibromophenylhydrazone was similarly treated, only 2 : 6-dibromoaniline and 8-bromo-1 : 2 : 3 : 4-tetrahydro-12-hydroxy*iso*carbazole (isolated as its picrate) were separated. Further, *cyclo*hexanone 2-chloro-1-naphthylhydrazone in boiling glacial acetic acid gave both 6-chloro-1 : 2 : 3 : 4-tetrahydro-7 : 8-benzocarbazole (IV) and 1 : 2 : 3 : 4-tetrahydro-12-hydroxy-7 : 8-benz*iso*carbazole (V). The structure of (IV) was proved both by its dehydrogenation, etc., to 1 : 2-benzocarbazole and by direct synthesis by cyclisation of *cyclo*hexanone 4-chloro-1-naphthylhydrazone.



(IV.) (V.) (VI.) (VII.)

Not only *cyclo*hexanone *o*-halogen-substituted hydrazones may yield 1 : 2 : 3 : 4-tetrahydro*iso*carbazoles: *cyclo*hexanone mesitylhydrazone forms 1 : 2 : 3 : 4-tetrahydro-6 : 8 : 12-trimethyl*iso*carbazole (isolated as its picrate) (unless migration of methyl occurs, which would yield a tetrahydrocarbazole).

It has already been reported (Barnes, Pausacker, and Schubert, *loc. cit.*) that *cyclo*hexanone *o*-chlorophenylhydrazone yields 8-chloro-1 : 2 : 3 : 4-tetrahydrocarbazole and 1 : 2 : 3 : 4-tetrahydro-12-hydroxy*iso*carbazole (VI). When an attempt was made to convert (VI) into the

corresponding 12-methoxy-compound (m. p. 146°), by treating it with methylmagnesium iodide followed by excess of methyl iodide, it was found that the product (m. p. 206°) had the correct empirical formula but did not contain a methoxyl group: the structure of this compound is uncertain. Further attempts to prepare (VI) or its analogues by the general method of Bloink and Pausacker (*J.*, 1950, 1328) failed. Thus 2-benzyloxy*cyclo*hexanone phenylhydrazone yielded 1-keto-1 : 2 : 3 : 4-tetrahydrocarbazole on sulphuric acid cyclisation, and 2-acetoxy-1 : 2 : 3 : 4-tetrahydro-1-ketonaphthalene gave 1 : 2 : 3 : 4-tetrahydro-1 : 2-diketonaphthalene bisphenylhydrazone in boiling alcohol and 1 : 4-dihydro-1-keto-2 : 3-benzocarbazole phenylhydrazone (VII) when kept in glacial acetic acid.

Cyclisation of *cyclo*hexanone *o*-bromophenylhydrazone was also investigated, as it was considered that (VI) would thus be formed, as the corresponding chloro-compound had already yielded this substance. However, different results were obtained. Along with 8-bromo-1 : 2 : 3 : 4-tetrahydrocarbazole (already isolated in the crude form by Barclay and Campbell, *J.*, 1945, 530), three other compounds, (*A*) $C_{12}H_{10}O_2NBr$, m. p. 146°, (*B*) $C_{12}H_{10}O_2NBr$, m. p. 166°, and (*C*) $C_{12}H_9ONBr$, m. p. 253°, were isolated by chromatographic separation. (*A*) displays neither basic nor phenolic properties, whereas (*B*) is soluble in sodium hydroxide solution and is a primary aromatic amine. In addition, (*B*) forms a monoacetyl derivative. When refluxed with alcoholic potash, (*A*) and (*B*) were converted, by loss of water, into (*C*). The substance (*C*) formed a monoacetyl derivative and was soluble in both warm hydrochloric acid and sodium hydroxide solution. When treated with hydrogen in presence of palladised charcoal at 300° it was converted into a strong base, $C_{12}H_{11}N$, m. p. 60°, which formed a picrate. This base did not appear to react with nitrous acid, signifying that it is a tertiary amine. When hydrogenated in the presence of Raney nickel and potassium hydroxide, (*C*) was converted into a basic phenol, $C_{12}H_{11}ON$.

Although the structures of (*A*), (*B*), and (*C*) have not been elucidated, it is of interest that their empirical formulæ * indicate that they may be derived from the *o*-bromoanilino-radical which would be expected if the reaction proceeds according to the mechanism proposed by Pausacker and Schubert (*J.*, 1949, 1384):

$$2C_6H_5NBr + H_2O \longrightarrow C_{12}H_9ONBr\ (C) + NH_4Br$$
$$2C_6H_5NBr + 2H_2O \longrightarrow C_{12}H_{10}O_2NBr\ (A \text{ or } B) + NH_4Br$$

Finally, results have been obtained similar to those reported by Pleininger (*Ber.*, 1950, **83**, 273), who found that α-ketobutyrolactone phenylhydrazone (VIII) is converted by hydrogen chloride into (IX), which is isomeric with (VIII) and is one of the postulated intermediates in

(VIII.) (IX.)

indole formation. We have similarly found that, when camphenilone phenylhydrazone is treated with hydrogen chloride in alcohol, a base is isolated (as its picrate and styphnate) which is isomeric with the original hydrazone and appears to have a structure analogous to that of Pleininger's imine intermediate.

Experimental.

Cyclisation of cyclo*Hexanone* 2 : 6-*Dichlorophenylhydrazone*.—The hydrazone (26·5 g.) was refluxed for 0·5 hour with concentrated sulphuric acid (28 ml.) and water (252 ml.) and then extracted with ether. The ethereal extract (22 g.) was dissolved in benzene and chromatographed on B.D.H. activated alumina. The zone (7·6 g.) which had a yellow fluorescence in ultra-violet light was eluted and treated with picric acid (7·5 g.) in benzene. The orange-red picrate was decomposed with excess of sodium hydroxide and distilled. It had b. p. 180°/0·5 mm., m. p. 67°, mixed m. p. with 6 : 8-dichloro-1 : 2 : 3 : 4-tetrahydrocarbazole 68°, and gave a *picrate*, m. p. 120° (from benzene) (Found: N, 12·1. $C_{12}H_{11}NCl_2,C_6H_3O_7N_3$ requires N, 11·9%), and *styphnate*, m. p. 104° (from light petroleum, b. p. 40—60°) (Found: N, 11·7. $C_{12}H_{11}NCl_2,C_6H_3O_8N_3$ requires N, 11·5%). A small fore-run (0·8 g.; b. p. 84°/1·2 mm.) was identical (mixed m. p.) with 2 : 6-dichloroaniline.

* It should be noted, however, that Rast molecular-weight determinations for (*B*) and (*C*) were not consistent with the formulæ assigned by us to these substances.

The intermediate dark green zone was discarded and the column eluted with alcohol, a fraction (8·7 g.) being obtained. Treatment of the solution with picric acid (8·4 g.) in benzene gave a *picrate*, red needles (from benzene), m. p. 159° (Found: N, 12·2. $C_{12}H_{12}ONCl,C_6H_3O_7N_3$ requires N, 12·4%). 8-*Chloro*-1 : 2 : 3 : 4-*tetrahydro*-12-*hydroxyisocarbazole* was isolated from the picrate by means of sodium hydroxide solution and had m. p. 127° (from light petroleum, b. p. 100—120°) (Found: N, 6·2; Cl, 16·4. $C_{12}H_{12}ONCl$ requires N, 6·3; Cl, 16·0%).

A chloride ion determination on the aqueous portion of the above reaction mixture indicated 33% of hydrolysis.

Cyclisation of cyclo*Hexanone* 2 : 6-*Dibromophenylhydrazone*.—Similar cyclisation of this hydrazone (30·6 g.) gave an ethereal extract (23·6 g.) which was distilled. The first fraction (b. p. 80°/0·2 mm.; m. p. 84°; 4·6 g.) was identified as 2 : 6-dibromoaniline (mixed m. p.). The second fraction (b. p. 150—155°/0·25 mm.; 6·7 g.) was treated with picric acid, to form 8-*bromo*-1 : 2 : 3 : 4-*tetrahydro*-12-*hydroxyisocarbazole picrate*, m. p. 130° (reddish-brown needles from benzene) (Found: N, 11·6. $C_{12}H_{12}ONBr,C_6H_3O_7N_3$ requires N, 11·3%). A bromide ion analysis on the aqueous portion of the mixture indicated 63% of hydrolysis.

Cyclisation of cyclo*Hexanone* 2-*Chloro*-1-*naphthylhydrazone*.—The hydrazone (33 g.) was refluxed (1·5 hour) with glacial acetic acid (280 ml.). The acetic acid was distilled on the water-bath (water-pump), and the residue dissolved in a small volume of benzene and chromatographed on alumina, with benzene as eluent. When this solution was evaporated, 6-*chloro*-1 : 2 : 3 : 4-*tetrahydro*-7 : 8-*benzocarbazole* (IV) was obtained, having m. p. 119° (from light petroleum, b. p. 60—90°) (Found: C, 75·4; H, 5·7; N, 5·3. $C_{16}H_{14}NCl$ requires C, 75·2; H, 5·5; N, 5·5%). The *picrate* had m. p. 168° (from benzene) (Found: N, 12·0. $C_{16}H_{14}NCl,C_6H_3O_7N_3$ requires N, 11·6%). When (IV) was treated with hydrogen and palladised charcoal at 300°, 1 : 2-benzocarbazole was obtained in excellent yield, having m. p. 228° (from light petroleum, b. p. 100—120°) (Found: N, 7·0. Calc. for $C_{16}H_{11}N$: N, 6·5%) [*picrate*, m. p. 184° (from benzene–light petroleum, b. p. 60—90°) (Found: N, 13·0. $C_{16}H_{11}N,C_6H_3O_7N_3$ requires N, 12·6%)].

When the column was finally eluted with benzene–ethyl alcohol (5%), 12-*hydroxy*-1 : 2 : 3 : 4-*tetrahydro*-7 : 8-*benzoisocarbazole*, m. p. 320° (from pyridine–ethyl alcohol), was deposited (Found: C, 81·3; H, 6·1; N, 6·0. $C_{16}H_{15}ON$ requires C, 81·0; H, 6·3; N, 5·9%).

The structure of (IV) was proved by synthesis: 1-chloro-4-nitronaphthalene was reduced with hydrogen in the presence of Raney nickel (yield, 90%), and the resultant 4-chloro-1-naphthylamine was converted into the corresponding hydrazine by Carlin and Fisher's method (*loc. cit.*) (yield of crude hydrazine, 75%). This (1·5 g.) and *cyclo*hexanone (1 g.) were refluxed for 1 hour with glacial acetic acid (30 ml.). On evaporation, (IV) (1·6 g.) was obtained, having m. p. and mixed m. p. with the product obtained above, 121°.

Cyclisation of cyclo*Hexanone Mesitylhydrazone*.—The above hydrazone was cyclised with glacial acetic acid, and the residue, after removal of the acetic acid under reduced pressure, was treated with picric acid in benzene. Black crystals of (?) 1 : 2 : 3 : 4-*tetrahydro*-6 : 8 : 12-*trimethylisocarbazole picrate*, m. p. 170—171° (from benzene), were obtained (Found: C, 57·1; H, 5·1; N, 12·7. $C_{15}H_{19}N,C_6H_3O_7N_3$ requires C, 57·2; H, 5·0; N, 12·7%).

Reaction of 1 : 2 : 3 : 4-*Tetrahydro*-12-*hydroxyisocarbazole* (VI) *with Methylmagnesium Iodide and Methyl Iodide*.—A filtered solution of methylmagnesium iodide [prepared from magnesium (0·5 g.), methyl iodide (1 ml.), and ether (10 ml.)] was added to a solution of (VI) (0·2 g.) in ether (10 ml.). After 1 hour's refluxing, methyl iodide (5 ml.) was added and refluxing continued for 2·5 hours. The solution was washed with ammonium chloride solution and evaporated, a *compound*, m. p. 206° (from ethyl acetate), being obtained (Found: C, 77·1; H, 7·3; N, 6·9; OMe, 0. $C_{13}H_{15}ON$ requires C, 77·6; H, 7·5; N, 7·0%).

Cyclisation of 2-*Benzyloxycyclohexanone Phenylhydrazone*.—2-*Benzyloxycyclohexanone*, prepared by heating 2-chlorocyclohexanone with sodium benzyloxide in anhydrous benzene, had b. p. 173—175°/21 mm. (Found: C, 76·8; H, 7·8. $C_{13}H_{16}O_2$ requires C, 76·5; H, 7·8%). When this was condensed with phenylhydrazine and cyclised with sulphuric acid, the product consisted almost entirely of neutral material—a mixture of benzyl alcohol and 1 : 2 : 3 : 4-tetrahydro-1-ketocarbazole (m. p. and mixed m. p. 168°).

Reactions of 2-*Acetoxy*-1 : 2 : 3 : 4-*tetrahydro*-1-*ketonaphthalene with Phenylhydrazine*.—A mixture of the ketone (1·0 g.) and phenylhydrazine (1·5 g.) in acetic acid (10 ml.) gradually deposited bright yellow needles (1·0 g.) of 1 : 4-*dihydro*-1-*keto*-2 : 3-*benzocarbazole phenylhydrazone*, m. p. 175° (from acetic acid) (Found: N, 12·9. $C_{22}H_{17}N_3$ requires N, 13·0%).

When the ketone (1·0 g.) was refluxed (3 days) with phenylhydrazine (1·6 g.) in ethyl alcohol (10 ml.), ammonia was evolved, but the only product isolated was 1 : 2 : 3 : 4-*tetrahydro*-1 : 2-*diketonaphthalene bisphenylhydrazone* which separated from the cooled mixture as yellow needles, m. p. 126° (from acetic acid) (Found: C, 77·2; H, 5·8; N, 16·1. $C_{22}H_{20}N_4$ requires C, 77·6; H, 5·9; N, 16·5%).

These results differ from those obtained by Bloink and Pausacker (*loc. cit.*).

Cyclisation of cyclo*Hexanone* o-*Bromophenylhydrazone*.—This hydrazone (48 g.) was refluxed for 10 minutes with a mixture of concentrated sulphuric acid (50 ml.) and water (450 ml.). The product was extracted with ether and basification of the acid solution gave an oil which was acetylated, forming N-*acetyl*-o-*bromophenylhydrazine*, m. p. 156° (from water) (Found: C, 41·6; H, 4·2; N, 12·1. $C_8H_9ON_2Br$ requires C, 41·5; H, 3·9; N, 12·2%). The ethereal extract, a dark red oil (46 g.), was dissolved in dry benzene and passed through a column (24″ × 1·5″) packed with activated alumina (Peter Spence; type H 100/200). The column was eluted with benzene, and the eluate, when kept,

deposited a solid (*A*) (3·2 g.; m. p. 146°). Concentration in the air gave a second solid (*B*) (3·0 g.; m. p. 166°). The column was then eluted with alcohol–benzene (1 : 20), giving a third substance (*C*) (2·15 g.; m. p. 252°). After (*A*) and (*B*) had been filtered off, the filtrate was evaporated to dryness, yielding a dark red oil (34 g.). A portion of this with picric acid yielded *8-bromo-1 : 2 : 3 : 4-tetrahydrocarbazole picrate*, m. p. 133° (red needles from benzene) (Found : C, 45·4; H, 3·5; N, 12·0. $C_{12}H_{12}NBr,C_6H_3O_7N_3$ requires C, 45·1; H, 3·1; N, 11·7%), which with sodium hydroxide solution afforded *8-bromo-1 : 2 : 3 : 4-tetrahydrocarbazole*, m. p. 57° [prisms from light petroleum (b. p. 40—60°)] (Found : N, 6·1. $C_{12}H_{12}NBr$ requires N, 5·6%).

When (*A*) or (*B*) (0·2 g.) was refluxed for 2 hours with ethyl alcohol (10 ml.) and potassium hydroxide (0·6 g.), (*C*) (identified by m. p. and mixed m. p.) was formed.

Chemical properties of (C). Substance (*C*) crystallised as needles (from benzene), m. p. 253° [Found : C, 54·5; H, 2·9; N, 5·2; Br, 29·2; *M* (Rast), 210. $C_{12}H_8ONBr$ requires C, 54·9; H, 3·1; N, 5·3; Br, 30·5%; *M*, 262], and gave a *semipicrate* (from benzene), m. p. 223—224° (Found : C, 48·1; H, 3·1; N, 9·5. $2C_{12}H_8ONBr,C_6H_3O_7N_3$ requires C, 47·8; H, 2·5; N, 9·3%). It was insoluble in cold water, dilute hydrochloric acid, or sodium hydroxide solution, but soluble in all these solvents when heated, a precipitate appearing when the aqueous and hydrochloric acid solutions were cooled. When the sodium hydroxide solution was acidified, a heavy precipitate was deposited. No reaction was noted with nitrous acid, followed by alkaline β-naphthol.

When (*C*) (0·2 g.) was heated at 280—300° for 3 hours with palladised charcoal (0·2 g.) in a stream of hydrogen, a white sublimate of a hydrobromide was obtained. This was extracted with water, the solution filtered, and the filtrate evaporated to dryness. The residue was treated with sodium hydroxide solution, and the *base* extracted with light petroleum (b. p. 40—60°). When purified by sublimation in a high vacuum, it had m. p. 60° (Found : C, 84·8; H, 6·8; N, 8·2. $C_{12}H_{11}N$ requires C, 85·2; H, 6·5; N, 8·3%). It dissolved readily in dilute hydrochloric acid and did not react with sodium nitrite followed by alkaline β-naphthol. It formed a *picrate* (yellow needles from water), m. p. 190° (Found : C, 54·3; H, 3·5; N, 14·0. $C_{12}H_{11}N,C_6H_3O_7N_3$ requires C, 54·2; H, 3·5; N, 14·1%). It gave a black tar when heated with benzenesulphonyl chloride and sodium hydroxide.

When (*C*) (0·4 g.) was shaken in an atmosphere of hydrogen at room temperature and pressure with Raney nickel (4 ml.) and potassium hydroxide (0·25 g.) in ethyl alcohol (20 ml.), 1·9 moles of hydrogen were absorbed. The *product*, m. p. 341° (from ethyl alcohol), which was soluble in both sodium hydroxide solution and hydrochloric acid, gave a red colour with ferric chloride in alcohol (Found : C, 77·9; H, 6·1; N, 7·3. $C_{12}H_{11}ON$ requires C, 77·7; H, 5·9; N, 7·6%).

Acetylation of (*C*) in pyridine–acetic anhydride and extraction with ether gave a *product*, m. p. 154° (from *n*-hexane), soluble in hydrochloric acid (Found : C, 55·7; H, 3·1; N, 5·0; Ac, 15·9. $C_{14}H_{10}O_2NBr$ requires C, 55·2; H, 3·3; N, 4·6; Ac, 14·2%).

Chemical properties of (B). Substance (*B*) was not isolated in every experiment. It formed needles (from benzene), m. p. 166° [Found : C, 51·5; H, 3·9; N, 5·1; Br, 23·8; *M* (Rast), 208. $C_{12}H_{10}O_2NBr$ requires C, 51·4; H, 3·6; N, 5·0; Br, 28·6%; *M*, 280). It was insoluble in water or dilute hydrochloric acid in the cold, but soluble in water on warming and gave an oil when heated with hydrochloric acid. It dissolved in sodium hydroxide solution, forming a lemon-yellow solution which gave a heavy precipitate on the addition of hydrochloric acid. When treated with nitrous acid and added to alkaline β-naphthol, a deep-red solution was obtained, indicating a primary aromatic amine soluble in sodium hydroxide. It gave neither a picrate nor a positive ferric chloride test. With pyridine–acetic anhydride it gave a *compound*, m. p. 124° (from light petroleum, b. p. 60—90°) (Found : C, 52·3; H, 4·2; N, 4·2; Ac, 15·3. $C_{14}H_{12}O_3NBr$ requires C, 52·2; H, 3·7; N, 4·4; Ac, 13·4%).

Chemical properties of (A). The substance had m. p. 146° (deflagration) (from dioxan) (Found : C, 51·2; H, 4·0; N, 4·8; Br, 28·6. $C_{12}H_{10}O_2NBr$ requires C, 51·4; H, 3·6; N, 5·0; Br, 28·6%). It was insoluble in hot or cold water, cold hydrochloric acid, or cold sodium hydroxide solution, but gave an oil when boiled with either of the last two reagents. It did not react with ferric chloride or nitrous acid.

Cyclisation of Camphenilone Phenylhydrazone.—Camphenilone (3·0 g.) and phenylhydrazine (2·4 g.) were heated on a boiling water-bath for 4 hours, under reduced pressure, in the presence of a drop of acetic acid. *Camphenilone phenylhydrazone* (4·0 g.) (b. p. 137—40°/0·2 mm.) was obtained (Found : C, 78·6; H, 8·7; N, 12·8. $C_{15}H_{20}N_2$ requires C, 78·9; H, 8·8; N, 12·3%). The hydrazone (3·9 g.) was dissolved in magnesium-dried ethyl alcohol (15 ml.) cooled in ice, and saturated with hydrogen chloride. After being cooled for 1 hour, the mixture was set aside over-night at room temperature, whereafter a solid had separated. After removal of the alcohol under reduced pressure, water was added and the neutral substance (3·2 g.) was extracted with ether. The aqueous filtrate was made alkaline with sodium hydroxide solution, ammonia being evolved, and the precipitated organic base (0·5 g.) was extracted with ether. It formed a *picrate*, m. p. 144° (decomp.) (from light petroleum, b. p. 80—100°) (Found : C, 55·0; H, 5·1. $C_{15}H_{20}N_2,C_6H_3O_7N_3$ requires C, 55·1; H, 5·1%) and a *styphnate*, m. p. 160° (decomp.) (from light petroleum, b. p. 100—120°) (Found : C, 52·9; H, 4·8; N, 14·3. $C_{15}H_{20}N_2,C_6H_3O_8N_3$ requires C, 53·3; H, 4·9; N, 14·8%).

Analyses are by Drs. Strauss and Weiler, Oxford, and Dr. Zimmermann, Melbourne. Determinations of bromine and acetyl were approximate only, but suffice to show the number of atoms present.

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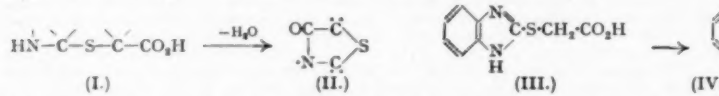
159. *Anhydro-compounds from Nitrogen-containing Derivatives of Thioglycollic Acid. Part I. Pyridine and Quinoline Compounds.*

By G. F. Duffin and J. D. Kendall.

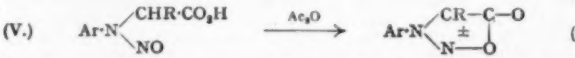
Like (2-pyridylthio)acetic acid (Koenigs and Geisler, *Ber.*, 1924, **57**, 2076), (2-quinolylthio)acetic acids unsubstituted in the 8-position react with acetic anhydride to give orange-yellow unimolecular anhydro-compounds. Similar, but less stable, compounds are obtained from α-(2-quinolylthio)-propionic and -*n*-butyric acids, but not from (4-quinolylthio)acetic acids. The properties of the anhydro-compounds are best explained on the basis of cyclic meso-ionic structures.

When a compound containing the system (I) is subjected to the action of a dehydrating agent, water is normally eliminated between the imino- and carboxyl groups, and a substituted thiazolidone (II) formed; *e.g.*, (2-benziminazolylthio)acetic acid (III), when heated with acetic anhydride, readily gives (IV) (Kendall and Duffin, B.P. 634,951).



(I.) (II.) (III.) (IV.)

If no hydrogen atom, or group which can be eliminated easily, is attached to the nitrogen atom in (I), ring closure of this type is impossible. Earl and Mackney (*J.*, 1935, 899) have shown, however, that *N*-aryl-*N*-nitrosoglycines (V), which contain the system O:N·N:CH·CO_2H, and cannot undergo normal ring closure without molecular rearrangement, are readily dehydrated by acetic anhydride to give unimolecular compounds now known as "sydnones." Baker, Ollis, and Poole (*J.*, 1949, 307; 1950, 1542) have proposed for these compounds a cyclic meso-ionic structure which is the hybrid of a number of contributing ionic forms and may be conveniently represented as (VI).



(V.) (VI.)

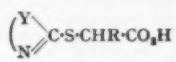
In the series of communications, of which this is Part I, the results are described of the action of dehydrating agents on various derivatives of thioglycollic acid which cannot undergo normal ring closure, *e.g.*, heterocyclic compounds of the type (VII) which contain the system ·N:C·S·C·CO_2H, and (arylazothio)acetic acids containing the system ·N:N·S·C·CO_2H. Although in some systems dehydration gives compounds with the characteristics of cyclic meso-ionic structures, yet the formation of these is not general, as shown in subsequent communications.

Koenigs and Geisler (*loc. cit.*) heated (2-pyridylthio)acetic acid (VIII) with acetic anhydride, and obtained a yellow compound which could be crystallised unchanged from ethanol, and which they regarded as the thiophen derivative (IX). Analysis indicated that the compound was formed by loss of a molecule of water from one molecule of the acid and it was unimolecular in phenol. With hydrochloric acid the anhydro-compound was reconverted into (VIII), and concentrated sulphuric acid gave 2-methylthiopyridine and carbon dioxide. Phenylhydrazine was reported to give a phenylhydrazone.

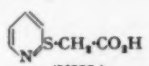
Tschitschibabin and Woroshtzow, jun. (*Ber.*, 1933, **66**, 364), showed that the anhydro-compound was not (IX) since it was insoluble in cold alkali, did not give a dye on oxidation, had a molecular weight in nitrobenzene double that of (IX), and even with water readily reverted to the original (2-pyridylthio)acetic acid. An unequivocal synthesis of (IX) also proved that this was different from the product obtained from (VIII), and it was shown that (3 : 5-dibromo-2-pyridylthio)acetic acid with acetic anhydride gave a dibromo-compound with similar properties to that obtained from (VIII). Tschitschibabin and Woroshtzow, therefore, regarded the yellow compound as a keten derivative (X) and attributed its stability towards ethanol to the presence of the tertiary amino-group (cf. Staudinger, *Ber.*, 1907, **40**, 1145). They ascribed their failure to obtain a similar type of anhydro-compound from (3-pyridylthio)-acetic acid to the 3-position in pyridine being unfavourable to keten formation.

When (2-quinolylthio)acetic acid is dissolved in acetic or propionic anhydride, and the solution warmed, it rapidly becomes deep yellow, and orange-yellow crystals separate. Similar

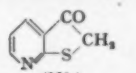
compounds are also obtained from other (2-quinolylthio)acetic acids with methyl substituents in both the pyridine and the benzene ring, provided, however, that no substituent is present in the 8-position. Reaction products are also obtained from α-(2-quinolylthio)-propionic and



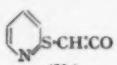
(VII.)



(VIII.)



(IX.)



(X.)

(Y = Remainder of heterocyclic nucleus.)

-*n*-butyric acids, but not from (4-quinolylthio)acetic acid. No reaction occurs when either ethyl (2-quinolylthio)acetate or (2-quinolylthio)acetamide is heated with acetic anhydride. Owing to difficulties of preparation of the acid, it has not yet proved possible to study the reaction between α-(2-quinolylthio)*iso*butyric acid and acetic anhydride.

The reaction between (2-quinolylthio)acetic acids and acetic anhydride is facilitated by a tertiary base, proceeding in the cold in the presence of pyridine, but is inhibited if a mineral acid is present. When inorganic dehydrating agents, *e.g.*, thionyl chloride or phosphoric oxide, are employed instead of acetic anhydride, no orange-yellow compounds are obtained, thionyl chloride and (2-quinolylthio)acetic acids giving, in pyridine, brown powders whose constitutions are still being investigated.

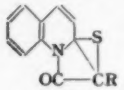
Analyses of the yellow compounds from α-(2-quinolylthio)-acids and acetic anhydride indicate that, like the product from (2-pyridylthio)acetic acid, they are anhydro-compounds formed by loss of one molecule of water from one molecule of acid. In general, they are insoluble in water and, with the exception of the products from α-(2-quinolylthio)-propionic and -butyric acids, sparingly soluble in cold organic solvents, but they can be recrystallised readily from hot ethanol or pyridine. When heated above their melting points, the anhydro-compounds darken and decompose. The anhydro-compound from (4-methyl-2-quinolylthio)acetic acid is, however, sufficiently stable for a molecular-weight determination by the Rast method, which indicates that the compound is unimolecular in camphor. Those compounds derived from (2-quinolylthio)acetic acids with a 4-methyl substituent appear to be the most stable, and those from α-(2-quinolylthio)-propionic and -*n*-butyric acids are least stable; *e.g.*, the latter are readily hydrolysed by water or dilute hydrochloric acid, whilst the former are unaffected even by hot concentrated hydrochloric acid. With 50% aqueous sulphuric acid all these anhydro-compounds are readily hydrated to the parent acids.

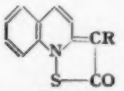
Because of its ease of preparation and relative stability, the anhydro-compound from (4-methyl-2-quinolylthio)acetic acid was selected for detailed study. Hydrolysis with aqueous-alcoholic sodium hydroxide gave mainly a mixture of 4-methylquinoline-2-thiol and another product, together with a trace of (4-methyl-2-quinolylthio)acetic acid. The second compound, which was soluble in hot, but insoluble in cold alkali, gave 2-hydroxy-4-methylquinoline on oxidation. Reduction of the anhydro-compound also gave 4-methylquinoline-2-thiol, and oxidation gave 2-hydroxy-4-methylquinoline. Unlike the anhydro-compound from (2-pyridylthio)acetic acid, that from (4-methyl-2-quinolylthio)acetic acid did not react with phenylhydrazine in acetic acid. In contradistinction to Koenigs and Geisler's statement, however, the compound isolated by us from the reaction between phenylhydrazine and the anhydro-compound from (2-pyridylthio)acetic acid did not appear to be a simple phenylhydrazone, its analysis indicating that it was formed from two molecules of the anhydro-compound and one molecule of phenylhydrazine with the loss of one molecule of water.

Although there is no ketonic activity, as indicated by the phenylhydrazone test, the anhydro-compounds, like quinones or *o*-diketones, *e.g.*, isatin and alloxan (Traube, *Ber.*, 1911, **44**, 3148; Schönberg, Moubasher, and Mostafa, *J.*, 1948, 176), readily react with benzylamine to give benzaldehyde, the appropriate quinoline-2-thiol being formed at the same time. A more detailed study of this reaction and its mechanism will be reported later.

From the conditions of formation of the anhydro-compounds from α-(2-quinolylthio)-acids, it is apparent that the system $N{:}\overset{|}{C}{\cdot}S{\cdot}\overset{|}{C}H{\cdot}CO_2H$ is essential for reaction, and that bonding of the nitrogen atom is involved since the steric influence of a group in the 8-position, or quaternary salt formation, inhibits reaction. The properties of the anhydro-compounds also indicate that, unless a reversible molecular rearrangement occurs on hydrolysis, the skeleton of the parent acids must be present in the anhydro-compounds. The formulation of a structure for the anhydro-compounds which accords with these facts is not simple. A linear keten formula of type (X), as suggested by Tschitschibabin and Woroshtzow for the anhydro-compound from

(2-pyridylthio)acetic acid, is clearly unsatisfactory, since it is unlikely that (*a*) a keten would be formed under the reaction conditions described, (*b*) such keten formation, if possible, would be inhibited by a methyl group in the 8-position, and (*c*) (4-quinolylthio)acetic acid, in which the electronic displacement is similar to that in (2-quinolylthio)acetic acid, would fail to give a


(XI.)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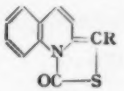
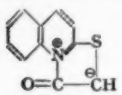

(XIII.)

keten under those conditions in which a keten is obtained from the latter acid. The steric effect of the 8-methyl group, the inhibition of anhydro-compound formation by quaternisation of the quinoline nitrogen atom, and the failure to obtain an anhydro-compound from (4-quinolylthio)acetic acid are, however, readily explicable on the basis of a cyclic structure containing the nitrogen atom. Such a structure, if purely covalent, might be represented by (XI) containing a three- and a four-membered ring system, or by (XII) or (XIII); (XI) is unsound on stereochemical grounds (cf. Baker *et al.*, *loc. cit.*, on the structures of the sydnones), whilst (XII) and (XIII) would involve an improbable molecular rearrangement which was reversible under conditions of hydrolysis.

Although a number of the reactions (*e.g.*, those with aqueous alkali and with benzylamine) of our anhydro-compounds are different from those of the sydnones, we consider that, like the sydnones, the anhydro-compounds are best represented by cyclic meso-ionic structures involving the hybrids of a number of resonance forms. These, like the resonance forms for the sydnones, may be formulated by (XIV)—(XX) which represent some of the dipolar contributors to the structure of the anhydro-compound from (2-quinolylthio)acetic acid. Alternatively, formula (XXI) may be used to indicate the hybrid. It will be noted that the sulphur in (XVII) bears a negative charge and has a valency shell expanded to ten electrons. A formula of this type containing a more extended conjugation might explain the colour of the anhydro-compound, and also the ease of its conversion into quinoline-2-thiol.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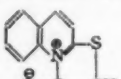
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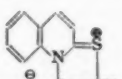
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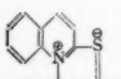
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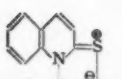
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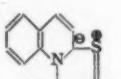
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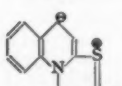
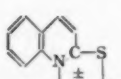

(XX.)


(XXI.)

The mechanism of formation of the anhydro-compounds by the action of acetic anhydride on α-(2-quinolylthio)acids is obscure. Baker *et al.* (*loc. cit.*) have suggested that the sydnones are formed from *N*-nitrosoglycines and acetic anhydride *via* mixed anhydrides, but it is not definite that such anhydrides are intermediates in our reaction, particularly as compounds like (4-pyridylthio)- and (4-quinolylthio)-acetic acids, which should also give mixed anhydrides, are recovered unchanged from boiling acetic anhydride.

Experimental.

Anhydro-compound from (2-Pyridylthio)acetic Acid.—A solution of (2-pyridylthio)acetic acid (1·5 g.) (Koenigs and Geisler, *loc. cit.*) in acetic anhydride (8 c.c.) was heated rapidly to boiling and then cooled; a mass of yellow crystals separated. Recrystallisation from ethanol gave yellow needles (1·0 g., 74%), m. p. 180°.

Action of Phenylhydrazine on Anhydro-compound from (2-Pyridylthio)acetic Acid.—When a solution of the anhydro-compound (1·0 g.) and phenylhydrazine (0·75 g.) in acetic acid (5·0 c.c.) was heated to boiling, it became red and a little hydrogen sulphide was evolved. On cooling, reddish crystals separated, which after recrystallisation gave pale red needles (0·1 g.), m. p. 163°. Dilution of the acetic acid solution precipitated more of the same *compound* (0·53 g.), m. p. 165°, in a buff-coloured form [Found: C, 61·2, 61·0; H, 4·2, 4·4; S, 16·05, 16·0. $C_{20}H_{16}ON_4S_2$ (= $2C_7H_5ONS + C_6H_8N_2 - H_2O$) requires C, 61·2; H, 4·1; S, 16·3%. Koenigs and Geisler's "phenylhydrazone" requires C, 64·75; H, 4·6; S, 13·3%].

Action of Acetic Anhydride on (4-*Pyridylthio*)*acetic Acid.*—A solution of (4-pyridylthio)acetic acid (0·9 g.) (King and Ware, *J.*, 1939, 875) in dry pyridine (5 c.c.) and acetic anhydride (5·5 c.c.) was heated at 100° for 1 hour. Some decomposition appeared to take place and the solution darkened. As nothing crystallised on cooling, the solution was concentrated to half bulk by heating at 60° under reduced pressure. On cooling, crystals were deposited (0·12 g.), of m. p. 255° (decomp.) raised to 265° (decomp.) by admixture with authentic (4-pyridylthio)acetic acid. Addition of water to the mother-liquors precipitated an oily mass from which a further small quantity of the acid was obtained by extraction with boiling water.

(2-*Quinolylthio*)*acetic Acid.*—Chloroacetic acid (3·1 g.) in 10% aqueous sodium hydroxide (13·2 c.c. was added to quinoline-2-thiol (5·3 g.) in 10% aqueous sodium hydroxide (13·2 c.c.). The solution was heated at 100° for 1 hour, filtered, and cooled to 0°, and concentrated hydrochloric acid (3·5 c.c.) added. (2-*Quinolylthio*)*acetic acid* separated as an oil, which crystallised when rubbed. After filtration and drying it was obtained from benzene–light petroleum as colourless needles (5·2 g., 73%), m. p. 90° (Found : C, 60·1; H, 4·0; S, 14·6. $C_{11}H_9O_2NS$ requires C, 60·25; H, 4·15; S, 14·6%).

By an analogous process other quinoline derivatives of thioglycollic acid, described below, were prepared.

Anhydro-compound from (2-*Quinolylthio*)*acetic Acid.*—(2-Quinolylthio)acetic acid (1·0 g.) was dissolved in acetic anhydride (5 c.c.) and the solution, which rapidly became deep yellow, was brought to the boil, and then cooled quickly. Addition of ethanol (25 c.c.) precipitated a mass of yellow crystals which were filtered off and recrystallised from pyridine–ethanol, giving yellow plates of the *anhydro*-compound (0·48 g., 52%), m. p. 194° (Found : S, 16·1; N, 6·85. $C_{11}H_7ONS$ requires S, 15·95; N, 6·95%).

Anhydro-compound from (4-*Methyl*-2-*quinolylthio*)*acetic Acid.*—(*a*) (4-*Methyl*-2-*quinolylthio*)*acetic acid*, prepared from 4-methylquinoline-2-thiol, was obtained from aqueous ethanol as pale yellow needles (86%), m. p. 117° (Found : S, 13·6; N, 6·2. $C_{13}H_{11}O_2NS$ requires S, 13·75; N, 6·0%). This acid (10 g.) in acetic anhydride (50 c.c.) was heated at 100° for 5 minutes, a deep yellow colour developing and a mass of yellow crystals separating. The mixture was cooled to room temperature and filtered, and the crystals were washed with ether, and recrystallised from pyridine, giving deep yellow plates of the *anhydro*-compound (6·8 g., 74%), m. p. 227° [Found : C, 66·9; H, 4·1; S, 14·65%; *M* (Rast), 210. $C_{13}H_9ONS$ requires C, 66·95; H, 4·2; S, 14·9%; *M*, 215]. The above experiment was repeated but with propionic anhydride instead of acetic anhydride, the same product (56%) being obtained.

(*b*) (4-Methyl-2-quinolylthio)acetic acid (2·0 g.) was dissolved with stirring at room temperature in a mixture of acetic anhydride (10 c.c.) and pyridine (10 c.c.). The temperature rose to 30°, and after 15 minutes the solution, which had become deep yellow, was poured into water (50 c.c.), a yellow solid being precipitated. After filtration, and washing with water and ether, the solid was recrystallised from pyridine as yellow plates (1·24 g., 69%), m. p. 227°, identical with those obtained in the above experiments.

Action of Acetic Anhydride on (4-*Methyl*-2-*quinolylthio*)*acetic Acid in the Presence of Hydrogen Chloride.*—(4-Methyl-2-quinolylthio)acetic acid (5·0 g.) was finely powdered and added to a solution of dry hydrogen chloride (1·0 g.) in acetic anhydride (25 c.c.). After 20 minutes' heating at 100°, the resulting dark green solution was cooled to 0°; a greenish precipitate was deposited which, after filtration, washing with ethanol, and drying, had m. p. 200—204° (3·4 g.). The solid was warmed for 5 minutes with aqueous N-sodium hydroxide (34 c.c.), and the solution filtered from a small quantity of coloured material and acidified, buff-coloured needles being slowly deposited (2·9 g.), m. p. 205—210°. The structure of this unidentified acidic substance is still being investigated.

3 : 4-*Dimethylquinoline*-2-*thiol.*—Thiourea (6·8 g.) was dissolved in boiling ethanol (130 c.c.) and 2-chloro-3 : 4-dimethylquinoline (16·5 g.) (Knorr, *Annalen*, 1888, **245**, 360) added. The solution was boiled for 8 hours and poured into water (200 c.c.), the ethanol removed by distillation, 33% aqueous sodium hydroxide (20 c.c.) added, and the mixture boiled for a further hour. After cooling to room temperature, the solution was filtered, and concentrated hydrochloric acid (20 c.c.) added, 3 : 4-*dimethylquinoline*-2-*thiol* being precipitated as a yellow solid. Recrystallisation from ethanol gave yellow needles (5 g., 30%), m. p. 223° (Found : C, 69·8; H, 5·9; S, 17·4. $C_{13}H_{11}NS$ requires C, 69·8; H, 5·85; S, 16·95%).

Anhydro-compound from (3 : 4-*Dimethyl*-2-*quinolylthio*)*acetic Acid.*—This *acid*, prepared from 3 : 4-dimethylquinoline-2-thiol, was obtained from aqueous ethanol as colourless needles (62%), m. p. 134° (Found : C, 63·1; H, 5·5; S, 12·8. $C_{13}H_{13}O_2NS$ requires C, 63·1; H, 5·3; S, 13·0%). It (1·0 g.) was heated with acetic anhydride (5 c.c.) on a steam-bath for 30 minutes. The deep yellow solution was cooled and diluted with ether; a solid separated, which, after filtration and recrystallisation from pyridine, gave the *anhydro*-compound as small brown needles with a blue lustre (0·37 g., 40%), m. p. 225° (Found : C, 68·1; H, 5·0; S, 13·9. $C_{13}H_{11}ONS$ requires C, 68·1; H, 4·85; S, 14·0%).

2-*Chloro*-4 : 8-*dimethylquinoline.*—2-Hydroxy-4 : 8-dimethylquinoline (Knorr, *Ber.*, 1884, **17**, 542) (20 g.) was boiled under reflux with phosphorus oxychloride (150 c.c.) until all solid had dissolved and the evolution of hydrogen chloride had ceased. Excess of the oxychloride was removed at 80° (bath)/40 mm. Water (500 c.c.) was added to the residue, and the resulting solution made alkaline by addition of 10% aqueous sodium hydroxide. 2-*Chloro*-4 : 8-*dimethylquinoline* was precipitated as a white solid which was filtered off and recrystallised from ethanol (charcoal) as white needles (16 g., 72%), m. p. 67° (Found : Cl, 16·65. $C_{11}H_{10}NCl$ requires Cl, 16·5%).

4 : 8-*Dimethylquinoline*-2-*thiol.*—2-Chloro-4 : 8-dimethylquinoline (14 g.) was added to a boiling solution of thiourea (5·6 g.) in ethanol (100 c.c.). The solution was boiled for 2 hours and diluted with water (200 c.c.), and the ethanol removed by distillation. The aqueous solution was filtered hot; on cooling, 4 : 8-*dimethylquinoline*-2-*thiol* crystallised as yellow plates (11·7 g., 83%), m. p. 195° (Found : C, 70·3; H, 5·6; S, 16·8. $C_{11}H_{11}NS$ requires C, 69·8; H, 5·85; S, 16·95%).

Acetic Anhydride and (4 : 8-*Dimethyl-2-quinolylthio*)*acetic Acid.*—This *acid* was obtained from 4 : 8-dimethylquinoline-2-thiol as colourless needles (66%), m. p. 132° (from aqueous ethanol) (Found : C, 63·15; H, 5·25; S, 12·9. $C_{13}H_{13}O_2NS$ requires C, 63·1; H, 5·3; S, 13·0%). The acid (2 g.) was heated with acetic anhydride (10 c.c.) for 2 hours at 100°. No yellow colour developed, and on cooling and addition of ether no solid separated. The ether was removed under reduced pressure, and the solution poured into water (50 c.c.), a colourless oil, which slowly crystallised, being precipitated. After filtration, the solid was recrystallised from aqueous ethanol, giving very pale yellow needles (1·7 g., 85% recovery), m. p. 132°, identical with (4 : 8-dimethyl-2-quinolylthio)acetic acid.

Anhydro-compound from α-(2-*Quinolylthio*)*propionic Acid.*—The *acid* was prepared from quinoline-2-thiol and α-bromopropionic acid, and crystallised from aqueous ethanol as pale yellow needles (68%), m. p. 101° (Found : C, 61·6; H, 4·99. $C_{12}H_{11}O_2NS$ requires C, 61·8; H, 4·75%). It (1 g.) was treated in pyridine (5 c.c.) at room temperature with acetic anhydride (5 c.c.); an intense orange-yellow colour developed and a mass of orange crystals rapidly separated. These were filtered off, washed with acetone, and dried to give very small orange-red crystals of the *anhydro*-compound (0·75 g., 80%), m. p. 148° (decomp.). Recrystallisation from light petroleum–benzene gave very small pale yellow needles which became red at 122° and had m. p. 148° (decomp.) (Found : C, 67·0; H, 4·25. $C_{12}H_9ONS$ requires C, 66·95; H, 4·2%).

Anhydro-compound from α-(2-*Quinolylthio*)*butyric Acid.*—The *acid* was prepared from quinoline-2-thiol and α-bromo-*n*-butyric acid, and obtained from aqueous ethanol as pale yellow needles (60%), m. p. 114° (Found : C, 63·1; H, 5·1; S, 12·9. $C_{13}H_{13}O_2NS$ requires C, 63·1; H, 5·3; S, 13·0%). It (1·0 g.) was dissolved in pyridine (5 c.c.) at room temperature, and acetic anhydride (5 c.c.) added; an intense orange-yellow colour developed; after a few minutes a mass of orange crystals separated. These were filtered off, washed well with acetone, and dried to give very small orange-red crystals (0·65 g., 72%). Recrystallisation from light petroleum–benzene gave the *anhydro*-compound as pale yellow crystals, m. p. 161—162° (decomp.) (Found : C, 68·05; H, 4·85; S, 14·0. $C_{13}H_{11}ONS$ requires C, 68·1; H, 4·85; S, 14·0%).

Anhydro-compound from α-(4-*Methyl*-2-*quinolylthio*)*propionic Acid.*—The required *acid* was prepared from α-bromopropionic acid and 4-methylquinoline-2-thiol, and obtained from aqueous ethanol as very pale yellow needles (64%), m. p. 139° (Found : C, 63·4; H, 5·1; S, 13·0. $C_{13}H_{13}O_2NS$ requires C, 63·1; H, 5·3; S, 13·0%). It (4·0 g.) was treated in pyridine (12 c.c.) at room temperature with acetic anhydride (12 c.c.). A deep orange colour developed and a mass of yellow needles rapidly separated. These were filtered off, washed with ether, and dried *in vacuo* (3·6 g., 78%), m. p. 134—135°. Recrystallisation from benzene (charcoal) gave bright orange needles of the *anhydro*-compound, m. p. 135—136°. The crystals contained a molecule of acetic acid of crystallisation which was not removed by repeated crystallisation (Found : C, 62·4; H, 5·3; N, 4·6; S, 10·8. $C_{13}H_{11}ONS,C_2H_4O_2$ requires C, 62·25; H, 5·25; N, 4·8; S, 11·1%).

Anhydro-compound from α-(4-*Methyl*-2-*quinolylthio*)-n-*butyric Acid.*—This *acid*, prepared from 4-methylquinoline-2-thiol and α-bromo-*n*-butyric acid, was obtained as pale yellow needles from aqueous ethanol (58%), m. p. 128° (Found : C, 64·3; H, 5·8; S, 12·2. $C_{14}H_{15}O_2NS$ requires C, 64·35; H, 5·8; S, 12·25%). It (1·0 g.) was dissolved in pyridine (4 c.c.)–acetic anhydride (4 c.c.) at room temperature. A deep orange colour rapidly developed and a mass of orange needles separated. These were filtered off, washed with ether, and dried *in vacuo* (0·7 g., 74%), m. p. 133—135°. Recrystallisation from benzene–light petroleum gave orange-yellow needles of the *anhydro*-compound, m. p. 139° (Found : C, 69·1; H, 6·0; S, 13·3; N, 5·65. $C_{14}H_{13}ONS$ requires C, 69·1; H, 5·4; S, 13·2; N, 5·75%).

Acid Hydrolysis of Anhydro-compound from (4-*Methyl*-2-*quinolylthio*)*acetic Acid.*—Finely powdered anhydro-compound (5 g.) was added to a mixture of concentrated sulphuric acid (10 c.c.) and water (10 c.c.). The resultant yellow solution was boiled gently under reflux for 10 minutes, the yellow colour disappearing. The solution was cooled, diluted with water (100 c.c.), and filtered to remove a trace of tarry solid, and an aqueous solution of sodium acetate (50 g.) added. A solid (5·2 g., 96%), m. p. 103—107°, was precipitated, which, on recrystallisation from aqueous ethanol gave pale yellow needles, m. p. 117° alone or admixed with authentic (4-methyl-2-quinolylthio)acetic acid (Found : S, 13·7; N, 6·0. Calc. for $C_{13}H_{11}O_2NS$: S, 13·75; N, 6·05%).

Alkaline Hydrolysis of Anhydro-compound from (4-*Methyl*-2-*quinolylthio*)*acetic Acid.*—The anhydro-compound (10 g.) was boiled under reflux with 40% aqueous sodium hydroxide (20 c.c.), water (100 c.c.), and ethanol (100 c.c.) for 10 hours, during which it slowly dissolved to give a brown solution. Ethanol (60 c.c.) was then removed by distillation, and the solution filtered hot (charcoal). On cooling, a pale brown micro-crystalline solid separated, which on recrystallisation from benzene gave colourless needles (3·0 g.), m. p. 210°. The compound was readily soluble in hot water and hot dilute aqueous sodium hydroxide but sparingly soluble in the cold (Found : C, 73·65, 73·45; H, 5·4, 5·6; S, 5·5, 4·9; N, 8·5%). The aqueous alkaline filtrate, diluted with a solution of sodium hydrogen carbonate (20 g.), deposited a pale yellow solid; this was filtered off, washed with water, and recrystallised from ethanol as pale yellow needles of 4-methylquinoline-2-thiol (4·5 g., 60%), m. p. 264—265° alone or admixed with the authentic compound. Acidification of the aqueous filtrate with excess of hydrochloric acid gave a solid (0·05 g.) which recrystallised from aqueous alcohol as pale yellow needles, m. p. 117° alone or admixed with authentic (4-methyl-2-quinolylthio)acetic acid.

The compound (1·0 g.), m. p. 210°, obtained from the original alkaline solution, was boiled for 3 hours with concentrated nitric acid (6 c.c.) and water (40 c.c.). After filtration the solution was cooled, and colourless crystals slowly separated. Recrystallisation from water gave colourless needles (0·62 g.), m. p. 227° alone or admixed with authentic 4-hydroxy-2-methylquinoline (Found : C, 75·15; H, 5·6. Calc. for $C_{10}H_9NO$: C, 75·4; H, 5·7%).

Reduction of Anhydro-compound from (4-*Methyl*-2-*quinolylthio*)*acetic Acid.*—(*a*) The anhydro-compound (10 g.) was boiled with concentrated hydrochloric acid (100 c.c.) and ethanol (400 c.c.), and

granulated zinc (40 g.) added. After 3 hours' heating a vigorous reaction occurred and the deep yellow colour of the solution faded. When the reaction had subsided the solution was filtered hot, and allowed to cool. Pale yellow crystals separated which, on recrystallisation from ethanol, gave pale yellow needles (4·0 g., 53%), m. p. 264—265°, alone or admixed with authentic 4-methylquinoline-2-thiol.

(*b*) A solution of the anhydro-compound (10 g.) in glacial acetic acid (100 c.c.) was warmed to 100°, and zinc dust (20 g.) added gradually; when the initial vigorous reaction had subsided the solution was filtered hot and allowed to cool, a copious pale yellow precipitate being deposited. This was filtered off, washed with acetone, and dried (7·0 g.). The solid, which had m. p. 281°, contained zinc and left a residue (20·4%) on ignition. It was dissolved in concentrated sulphuric acid (20 c.c.) at 0°, and the solution filtered from a sludge and poured on ice; a yellow solid was precipitated, which was collected and recrystallised from ethanol, giving pale yellow needles of 4-methylquinoline-2-thiol (2·95 g.), m. p. 264°.

Oxidation of Anhydro-compound from (4-*Methyl*-2-*quinolylthio*)*acetic Acid.*—(*a*) The anhydro-compound (10 g.) was boiled with concentrated nitric acid (60 c.c.) and water (400 c.c.) for 1 hour; the evolution of nitrous fumes had then ceased and the solid had dissolved completely. On cooling to 0°, a mass of white crystals slowly separated. These were filtered off and recrystallised from water as colourless needles (3·7 g., 55%), m. p. 227° alone or admixed with authentic 2-hydroxy-4-methylquinoline.

(*b*) The anhydro-compound (10 g.) was boiled with a solution of chromium trioxide (20 g.) and concentrated sulphuric acid (35 c.c.) in water (500 c.c.) for 3 hours; all the solid had then dissolved, and the solution was filtered hot and allowed to cool. A mass of crystals (4·9 g., 72%), m. p. 218—220°, was deposited which on recrystallisation from water gave colourless needles of 2-hydroxy-4-methylquinoline (2·1 g.), m. p. 227° (Found: C, 75·8; H, 5·8; N, 8·45. Calc. for $C_{10}H_9ON$: C, 75·4; H, 5·7; N, 8·8%).

Acid Hydrolysis of Anhydro-compound from α-(4-*Methyl*-2-*quinolylthio*)*butyric Acid.*—The anhydro-compound (1·0 g.) was added to concentrated hydrochloric acid (5 c.c.); a colourless solution was rapidy obtained which was evaporated to dryness, giving a pale yellow solid. The solid was dissolved in water (10 c.c.), and when kept the solution slowly precipitated pale yellow needles (0·92 g., 86%), m. p. 128° alone or admixed with authentic α-(4-methyl-2-quinolylthio)-*n*-butyric acid. Under similar conditions the anhydro-compound from α-(4-methyl-2-quinolylthio)propionic acid was also hydrolysed to the acid.

β-(2-*Quinolylthio*)*propionic Acid.*—To quinoline-2-thiol (4·83 g.) dissolved in aqueous potassium hydroxide (1·68 g. in 10 c.c. of water), β-chloropropionic acid (3·25 g.) in aqueous potassium hydroxide (1·68 g. in 10 c.c. of water) was added. The mixture was boiled for 4 hours, filtered hot, diluted with water, and acidified with concentrated hydrochloric acid (3 c.c.); a yellow oil was precipitated, which was dissolved in a mixture of benzene (50 c.c.) and ether (50 c.c.), and the solution extracted with 5% aqueous sodium hydrogen carbonate (3 × 50 c.c.). Acidification of the combined extracts gave a yellow *compound* which recrystallised from aqueous ethanol as pale yellow needles (2·3 g., 33%), m. p. 87° (Found: C, 61·7; H, 4·55; S, 14·1. $C_{12}H_{11}O_2NS$ requires C, 61·7; H, 4·75; S, 13·75%).

Failure of Acetic Anhydride to react with β-(2-*Quinolylthio*)*propionic Acid.*—A solution of this acid (1·0 g.) in acetic anhydride was heated at 100° for 1 hour. No change in colour occurred. After cooling, the solution was diluted with water, precipitating an oil which slowly crystallised in pale yellow needles (0·81 g.), m. p. 87° alone or admixed with the starting material.

Ethyl (2-*Quinolylthio*)*acetate.*—Quinoline-2-thiol (8·05 g.) was dissolved in a solution of sodium (1·15 g.) in ethanol (100 c.c.) and heated to boiling whilst ethyl chloroacetate (10·5 c.c.) was added dropwise during 10 minutes. The mixture was boiled for 3 hours, the precipitated sodium chloride removed by hot filtration, and the filtrate cooled; *ethyl* (2-*quinolylthio*)*acetate* separated as pale yellow needles (4·3 g., 35%), m. p. 91·5°, unchanged by recrystallisation from ethanol (Found: C, 62·9; H, 5·6; S, 13·1. $C_{13}H_{13}O_2NS$ requires C, 63·1; H, 5·3; S, 13·0%).

Failure of Acetic Anhydride to react with Ethyl (2-*Quinolylthio*)*acetate.*—Ethyl (2-quinolylthio)acetate (1·0 g.) was dissolved in acetic anhydride (10 c.c.), and the solution boiled for 1 hour. No yellow colour developed and, on cooling, a mass of colourless needles was deposited, which after filtration and drying gave unchanged ethyl (2-quinolylthio)acetate (0·48 g.), m. p. 91·5°. Dilution of the filtrate with warm water gave a further quantity (0·47 g.) of the same compound.

(2-*Quinolylthio*)*acetamide.*—Quinoline-2-thiol (7·5 g.) was dissolved in a solution of sodium (1·04 g.) in ethanol (20 c.c.) and heated to boiling whilst a suspension of chloroacetamide (4·36 g.) in ethanol (20 c.c.) was added. The mixture was boiled for 3 hours and filtered hot to remove precipitated sodium chloride, and the filtrate cooled; (2-*quinolylthio*)*acetamide* separated as colourless needles (5·5 g., 58%), m. p. 126°, unchanged by recrystallisation from ethanol (Found: C, 60·1; H, 4·55; S, 14·7. $C_{11}H_{10}ON_2S$ requires C, 60·5; H, 4·6; S, 14·7%).

Non-reaction of Acetic Anhydride with (2-*Quinolylthio*)*acetamide.*—This amide (2·0 g.) was boiled under reflux with acetic anhydride (10 c.c.) for 30 minutes. There was neither development of colour nor precipitation, on cooling. The solution was diluted with ethanol and evaporated under reduced pressure, and the residual oil washed with a little ethanol, whereupon it crystallised. The crystals were filtered off and dried (1·9 g.), m. p. 100—107°; recrystallisation from benzene–light petroleum gave colourless needles, m. p. 126° (1·4 g., 70% recovery), identical with the starting material.

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160. *Some Unsymmetrically Substituted αβ-Diethylstilbenes.*

By F. P. Jenkins and J. H. Wilkinson.

A number of unsymmetrical αβ-diethylstilbenes have been prepared for examination as potential inhibitors of œstrogenic activity. 3- and 4-Amino-α-ethyl-4′-methoxydeoxybenzoin were converted into 3- and 4-amino-αβ-diethyl-4′-methoxystilbene, of which the former underwent demethylation to the 4′-hydroxy-derivative much more readily than the latter. 4-Amidino- and 4-propionyl-αβ-diethyl-4′-methoxystilbene were prepared from the appropriate 4-cyano-stilbene and 4-*p*-cyanophenyl-3-*p*-methoxyphenylhexan-3-ol, respectively. 3-*p*-Aminophenyl-3-*p*-hydroxyphenylhexan-3-ol was obtained by treatment of 4-acetamido-4′-acetoxy-α-ethyldeoxybenzoin with excess of ethylmagnesium iodide.

None of these compounds exhibited anti-œstrogenic activity in mice. The aminohydroxystilbenes and 4-*p*-aminophenyl-3-*p*-hydroxyphenylhexan-3-ol were œstrogenic.

The marked success which attended the introduction of the synthetic œstrogen, diethylstilbœstrol, by Dodds *et al.* (see, *e.g.*, *Proc. Roy. Soc.*, 1939, *B*, **127**, 140; 1940, **128**, 253; 1944, **132**, 83) led us to prepare a number of unsymmetrically substituted analogues in the hope that the change of substituent might produce anti-œstrogenic activity. Apart from a considerable number of mono-ethers and mono-esters and some ether-esters, relatively few analogues having different groups in the 4- and 4′-positions have been described (cf. Solmssen, *Chem. Reviews*, 1945, **37**, 481; Masson, *Rev. Canad. Biol.*, 1944, **3**, 491). Jaeger and Robinson (*J.*, 1941, 744) prepared 4-acetyl-αβ-diethyl-4′-hydroxystilbene (I; R = Ac, R′ = OH) which was examined for progestational activity; Dodds, Golberg, Lawson, and Robinson (*Proc. Roy. Soc.*, 1939, *B*, **127**, 140) tested the 4-hydroxy-derivative (I; R = OH, R′ = H) for œstrogenic activity; Neher and Miescher (*Helv. Chim. Acta*, 1946, **29**, 449) prepared the carboxylic acids (I; R = OH, R′ = CO_2H) and (I; R = OMe, R′ = CO_2H), and Linnell and Sharma (*Quart. J. Pharm.*, 1941, **14**, 259) reported that αβ-diethyl-3 : 4′-dihydroxystilbene (II; R = R′ = OH) was œstrogenic.

Very few basic unsymmetrical diethylstilbenes have been described. Rubin and Wishinsky (*J. Amer. Chem. Soc.*, 1944, **66**, 1948) prepared 4-amino-αβ-diethyl-4′-hydroxystilbene (I; R = NH_2, R′ = OH); Haddow, Harris, Kon, and Roe (*Trans. Roy. Soc.*, 1948, **241**, *A*, 147, 187) examined the effect, on the growth of mouse tumours, of 4-dimethylamino-αβ-diethylstilbene (I; R = NMe_2, R′ = H), and the antibacterial properties of 4-amino-αβ-diethylstilbene (I; R = NH_2, R′ = H) were studied by Brownlee, Copp, Duffin, and Tonkin (*Biochem. J.*, 1943, **37**, 572).

In view of the ease with which the amino-group can be replaced by other substituents, we decided to prepare the 3- and the 4-amino-compound. In addition, since 4-acetyl-αβ-diethyl-4′-hydroxystilbene (Jaeger and Robinson, *loc. cit.*) was reported to have œstrogenic activity of a very low order, the corresponding 4-propionyl derivative appeared worth examining for anti-œstrogenic activity.

For the preparation of the 3- and 4-amino-αβ-diethyl-4′-hydroxystilbenes, Rubin and Wishinsky's route was employed. The Friedel–Crafts reaction of *m*- and *p*-nitrophenylacetyl chlorides with anisole gave the required 4′-methoxy-3- and -4-nitrodeoxybenzoins which were ethylated by Rubin and Wishinsky's method (*loc. cit.*). Reduction of the nitro-groups with stannous chloride or catalytically gave the corresponding aminodeoxybenzoins, and these, on treatment with ethylmagnesium halides, gave the diethylstilbenes (I and II; R = NH_2, R′ = OMe); the latter was readily demethylated by means of hydriodic acid, but the former gave very poor yields of the aminophenol by this method.

4-*p*-Aminophenyl-3-*p*-hydroxyphenylhexan-3-ol was prepared from 4-amino-α-ethyl-4′-methoxydeoxybenzoin, which readily underwent demethylation with hydrobromic acid. The resulting 4-hydroxy-derivative, however, formed an insoluble complex with ethylmagnesium

iodide from which the starting material was recovered unchanged. The *ON*-dibenzoyl derivative proved insufficiently soluble in ether or anisole, but the more soluble *ON*-diacetyl compound, on treatment with 5 moles of the Grignard reagent, gave the required hexanol or its *N*-acetyl derivative according to the conditions.

αβ-Diethyl-4-methoxy-4′-propionylstilbene (I; R = COEt, R′ = OMe) was prepared from 4-cyano-α-ethyl-4′-methoxydeoxybenzoin by a method similar to that used by Jaeger and Robinson (*loc. cit.*) for the 4-acetyl derivative. The 4-methoxy-4′-propionyl derivative, however, proved much more resistant to hydriodic acid demethylation than Jaeger and Robinson's compound, and we were unable to isolate the corresponding phenol.

4-Cyano-αβ-diethyl-4′-methoxystilbene (Neher and Miescher, *loc. cit.*) reacted with methanolic hydrogen chloride to give the corresponding imino-ether hydrochloride, which on treatment with alcoholic ammonia was converted into 4-amidino-αβ-diethyl-4′-methoxystilbene hydrochloride.

3- and 4-Amino-αβ-diethyl-4′-hydroxystilbene, 3-*p*-aminophenyl-3-*p*-hydroxyphenylhexan-3-ol, 4-amidino-αβ-diethyl-4′-methoxystilbene hydrochloride, and αβ-diethyl-4-methoxy-4′-propionylstilbene were tested for anti-œstrogenic activity in mice by the vaginal smear method, but none was active. With the exception of the amidine, all these compounds were œstrogenic. The œstrogenic activity of the hexanol is a result of some interest since it appears that no other hexanols of this series have been reported active in this respect. The following table, based upon figures kindly determined by Mrs. M. M. Boycott, B.Sc., shows the dose–response relations obtained.

Œstrogenic response in mice.

(The compounds were injected subcutaneously in two equal portions separated by an interval of 24 hours.)

Compound.	Solvent.	Total dose (mg.).	Response, %.
3-Amino-αβ-diethyl-4′-hydroxystilbene	Arachis oil	1	100
4-Amino-αβ-diethyl-4′-hydroxystilbene *	do.	1	100
		0·1	100
		0·01	50
4-*p*-Aminophenyl-3-*p*-hydroxyphenylhexan-3-ol ...	do.	1	100
		0·1	78
		0·01	0
αβ-Diethyl-4-methoxy-4′-propionylstilbene	do.	1	100
4-Amidino-αβ-diethyl-4′-methoxystilbene hydrochloride	Water	1	0

* Rubin and Wishinsky (*loc. cit.*) report that 7·5 γ of this compound were equivalent in œstrogenic potency to one Allen–Doisy rat unit.

Experimental.

(Analyses are by Drs. Weiler and Strauss, Oxford. M. p.s are uncorrected.)

4′-Methoxy-3-nitrodeoxybenzoin.—*m*-Nitrophenylacetic acid (13 g.) was converted into the chloride by treatment with thionyl chloride as described by Linnell and Roushdi (*Quart. J. Pharm.*, 1941, **14**, 270). The acid chloride in anisole (20 c.c.) was treated with powdered aluminium chloride (15 g.) at > 20°. The mixture was set aside for 24 hours with occasional shaking, then heated at 60° for 2 hours. After decomposition with 2N-hydrochloric acid and ice, the mixture was steam-distilled to remove the excess of anisole. The aqueous layer was decanted, and the residue washed successively with 2N-hydrochloric acid and water. On treatment with ether, the oil solidified to a crystalline solid, m. p. 83—84°. Recrystallisation from alcohol gave the required 4′-methoxy-3-nitrodeoxybenzoin (10·1 g., 52%) in pale yellow needles, m. p. 84—85°, unaffected by further crystallisation. Linnell and Roushdi (*loc. cit.*) report m. p. 85—86°.

α-Ethyl-4′-methoxy-3-nitrodeoxybenzoin.—4′-Methoxy-3-nitrodeoxybenzoin (13·1 g.) in absolute ethanol (100 c.c.) was treated with a solution of sodium ethoxide, prepared from sodium (1·2 g.) and ethanol (30 c.c.). Ethyl bromide (7·3 g.) was added, and the mixture heated under reflux for 2 hours. The alcohol was removed by steam-distillation, and the oily residue extracted with ether. Distillation gave the required *product* (12·5 g., 87%) as a pale yellow viscous oil, b. p. 180—181·5°/0·1 mm. (Found: C, 68·4; H, 5·7; N, 4·95. $C_{17}H_{17}O_4N$ requires C, 68·3; H, 5·7; N, 4·7%).

3-Amino-α-ethyl-4′-methoxydeoxybenzoin.—A solution of the foregoing compound (6·4 g.) in alcohol (25 c.c.) was treated with stannous chloride (15·2 g.) and 7N-hydrochloric acid (45 c.c.) and heated under reflux for 1½ hours. The cooled mixture was poured into excess of 10N-sodium hydroxide, and the oil extracted with ether. The ethereal solution was extracted with 4N-hydrochloric acid, and the acid layer made alkaline with sodium hydroxide. The oil was extracted with ether, dried (Na_2SO_4), and distilled. *3-Amino-α-ethyl-4′-methoxydeoxybenzoin* (4·57 g., 80%) was obtained as a pale yellow glass, b. p. 179·5—181°/0·1 mm., which gave pale yellow crystals, m. p. 122—124°, on treatment with ether (Found: C, 75·4; H, 6·8; N, 5·35. $C_{17}H_{19}O_2N$ requires C, 75·8; H, 7·1; N, 5·2%). The *benzoyl* derivative crystallised from alcohol in fine colourless needles, m. p. 174° (Found: C, 77·4; H, 6·1; N, 3·8. $C_{24}H_{23}O_3N$ requires C, 78·0; H, 6·0; N, 3·6%

3-*Amino-α-ethyl-4′-hydroxydeoxybenzoin.*—3-Amino-α-ethyl-4′-methoxydeoxybenzoin (0·7 g.) was heated in acetic acid (3 c.c.) under reflux with 48% hydrobromic acid (2 c.c.) for 1½ hours. After removal of the acids by distillation, the residue was neutralised with sodium carbonate and extracted with ether. The ethereal layer was extracted with 2N-sodium hydroxide, and the aqueous layer heated to expel ether. Acidification with acetic acid gave *3-amino-α-ethyl-4′-hydroxydeoxybenzoin* (0·53 g., 79%), which crystallised from 60% alcohol in brown plates, m. p. 150—151° (Found : C, 75·4; H, 6·7; N, 5·75. $C_{16}H_{17}O_2N$ requires C, 75·3; H, 6·7; N, 5·5%).

3-*Amino-αβ-diethyl-4′-methoxystilbene.*—3-Amino-α-ethyl-4′-methoxydeoxybenzoin (4·05 g.) in anhydrous ether (30 c.c.) was added during 1 hour to a solution of the Grignard reagent, prepared from magnesium (1·08 g.), ethyl iodide (7 g.), and anhydrous ether (20 c.c.), mechanical stirring being employed. Stirring was continued for a further 3 hours, and next morning the mixture was decomposed with ammonium chloride solution. The ethereal layer was washed with water and dried (Na_2SO_4). The solvent was removed but, when distillation of the residue was attempted, partial dehydration of the 4-*m*-aminophenyl-3-*p*-methoxyphenylhexan-3-ol occurred, so the residue was heated at 200°/20 mm. for 1 hour to complete the conversion into the required *stilbene*, which distilled at 149—151°/0·1 mm. and was obtained as a pale yellow oil (3·03 g., 72%), which darkened on storage (Found : C, 80·9; H, 8·1; N, 5·0. $C_{18}H_{23}ON$ requires C, 81·2; H, 8·2; N, 5·0%).

3-*Amino-αβ-diethyl-4′-hydroxystilbene.*—A mixture of the foregoing stilbene (2 g.), acetic acid (6 c.c.), and 48% hydrobromic acid (6 c.c.) was heated under reflux for 2 hours, and the acids were then removed. The gummy residue was neutralised with sodium carbonate and washed with water. It was dissolved in ether and extracted with 2N-sodium hydroxide, and the alkaline solution acidified with acetic acid. The *product* (1·07 g., 56%) was extracted with ether and distilled, b. p. 220—230° (air-bath)/0·1 mm., to give a pale yellow glass which became brown on storage. On treatment with ether it slowly crystallised. Recrystallisation from methanol gave colourless crystals, m. p. 163—164° (Found : C, 80·2; H, 7·85; N, 5·25. $C_{18}H_{21}ON$ requires C, 80·9; H, 7·9; N, 5·25%).

4′-Methoxy-4-nitrodeoxybenzoin was prepared from *p*-nitrophenylacetyl chloride [from the acid (181 g.)], anisole (260 c.c.), and aluminium chloride (200 g.) by a method similar to that used for the 3-nitro-isomer. This procedure was more convenient and gave higher yields than that of Rubin and Wishinsky (*loc. cit.*). After storage at room temperature overnight, the mixture was heated to 60° for 4 hours with frequent shaking. The cooled solution was poured into a mixture of ice (800 g.) and hydrochloric acid (*d* 1·16; 200 c.c.). The oily solid which separated was drained and triturated several times with water, then with alcohol (200 c.c.). The solid obtained was heated under reflux with alcohol (1 l.); the mixture was cooled, and the crystalline solid separated by decantation. Recrystallisation from alcohol gave the required product, m. p. 110—111°, raised to 114° by a second recrystallisation from alcohol (Found : C, 66·4; H, 4·85; N, 5·4. Calc. for $C_{15}H_{13}O_4N$: C, 66·4; H, 4·8; N, 5·2%); the yield was 204 g. (83%). Rubin and Wishinsky (*loc. cit.*) report m. p. 117—118°. The 2 : 4-*dinitrophenylhydrazone* crystallised from acetic acid in orange needles, m. p. 212° (Found : N, 15·1. $C_{21}H_{17}O_7N_5$ requires N, 15·5%).

4-*Amino-4′-methoxydeoxybenzoin.*—4′-Methoxy-4-nitrodeoxybenzoin (2·71 g.) was hydrogenated in benzene (30 c.c.) at 20° under atmospheric pressure in the presence of Adams's platinum oxide (0·3 g.); the uptake after 20 minutes was 750 c.c. (Calc. : 720 c.c.). The catalyst was removed, and the filtrate shaken with 2N-hydrochloric acid to precipitate the hydrochloride of the product. The solid was dissolved in hot water and converted into the required *base* by treatment with alkali. Recrystallisation from alcohol gave buff-coloured needles, m. p. 136—137° (Found : C, 74·5; H, 6·2; N, 5·8. $C_{15}H_{15}O_2N$ requires C, 74·7; H, 6·2; N, 5·8%). The *acetyl* derivative crystallised from alcohol in colourless needles, m. p. 175° (Found : C, 71·9; H, 6·0; N, 5·1. $C_{17}H_{17}O_3N$ requires C, 72·1; H, 6·0; N, 4·95%).

α-Ethyl-4′-methoxy-4-nitrodeoxybenzoin, prepared in 84% yield substantially as described by Rubin and Wishinsky (*loc. cit.*), had b. p. 198—201°/0·1 mm. (lit., 210—215°/0·8 mm.) (Found : C, 68·6; H, 5·75. Calc. for $C_{17}H_{17}O_4N$: C, 68·3; H, 5·7%). When excess of sodium ethoxide and ethyl iodide were employed, as used by Jaeger and Robinson (*loc. cit.*) for the corresponding 4-cyano-compound, some decomposition occurred, and varying amounts of an unidentified yellow mobile liquid, b. p. 76—81°/0·3 mm., 261°/760 mm., n_D^{25} 1·437, were formed (Found : C, 66·5; H, 7·45; N, 3·5%). Also the main product was contaminated with *p*-anisic acid, m. p. 184° (Found : C, 63·3; H, 5·05. Calc. for $C_8H_8O_3$: C, 63·2; H, 5·25%).

4-*Amino-α-ethyl-4′-methoxydeoxybenzoin.*—α-Ethyl-4′-methoxy-4-nitrodeoxybenzoin (15 g.) was hydrogenated in benzene (50 c.c.) at 20°/1 atm. in the presence of Adams's platinum oxide (0·3 g.) : hydrogen uptake was 3770 c.c. (Calc. : 3640 c.c.). The catalyst was filtered off, and the filtrate shaken with 5N-hydrochloric acid (30 c.c.). The sparingly soluble hydrochloride formed a gummy precipitate which hardened overnight. After being washed with benzene and ether it was triturated with 2N-sodium hydroxide (100 c.c.). The base was extracted with ether and dried (Na_2SO_4), and the solvent removed. The residue (12·9 g., 95%), a pale brown viscous oil, crystallised on storage to a buff-coloured solid, which after crystallisation from ether had m. p. 100—101° (Found : C, 75·7; H, 7·1; N, 5·15. Calc. for $C_{17}H_{19}O_2N$: C, 75·8; H, 7·1; N, 5·2%). Rubin and Wishinsky (*loc. cit.*) report m. p. 97—98·5°. The *benzoyl* derivative crystallised from alcohol in colourless clusters, m. p. 164° (Found : C, 77·0; H, 6·3; N, 3·9. $C_{24}H_{23}O_3N$ requires C, 77·2; H, 6·15; N, 3·75%).

4-*Amino-α-ethyl-4′-hydroxydeoxybenzoin.*—4-Benzamido-α-ethyl-4′-methoxydeoxybenzoin (43·8 g.) was heated in acetic acid (145 c.c.) under reflux with 48% hydrobromic acid (190 c.c.) for 3 hours. The *product*, isolated as described for 3-amino-α-ethyl-4′-hydroxydeoxybenzoin, crystallised from aqueous alcohol in colourless plates, m. p. 113—114° (Found : C, 75·1; H, 6·75; N, 5·3%). The *diacetyl* derivative separated from 60% alcohol in colourless needles, m. p. 113—114° (Found : C, 70·5; H, 6·3; N, 4·25. $C_{20}H_{21}O_4N$ requires C, 70·8; H, 6·2; N, 4·15%). The *dibenzoyl* derivative crystallised

from alcohol in fine colourless needles, m. p. 230—231°, sparingly soluble in most organic solvents (Found C, 77·6; H, 5·4. $C_{26}H_{25}O_4N$ requires C, 77·8; H, 5·4%). An attempt was made to convert the amino-phenol into the corresponding cyanophenol, but, after treatment of the diazo-solution with cuprous cyanide, the product did not give satisfactory analytical results.

4-Amino-αβ-diethyl-4′-methoxystilbene was prepared by Rubin and Wishinsky's method (*loc. cit.*), 4-*p*-aminophenyl-3-*p*-methoxyphenylhexan-3-ol (m. p. 112°, lit. 113—114°) being isolated as an intermediate (Found : C, 76·2; H, 8·2; N, 4·9. Calc. for $C_{19}H_{15}O_2N$: C, 76·3; H, 8·35; N, 4·7%). At 200°/20 mm., the hexanol underwent dehydration to the required stilbene, b. p. 176—177°/0·3 mm. (Found : C, 81·2; H, 8·0; N, 4·95. Calc. for $C_{19}H_{23}ON$: C, 81·2; H, 8·2; N, 4·95%). The American workers report b. p. 180—182°/1 mm.

4-Amino-αβ-diethyl-4′-hydroxystilbene.—The 4-amino-4′-methoxy-compound was demethylated by the method described for the 3-amino-derivative, but the yield was markedly inferior to that obtained by the method of Rubin and Wishinsky, who report b. p. 180—185°/0·1 mm. Our product had b. p. 200—202°/0·7 mm. (Found : C, 80·4; H, 8·0; N, 5·25. Calc. for $C_{18}H_{21}ON$: C, 80·9; H, 7·9; N, 5·25%). After storage for several weeks the viscous oily product deposited crystals which were collected and recrystallised successively from methanol and light petroleum (b. p. 80—100°). Colourless aggregations, m. p. 134—137°, were obtained. Admixture with authentic *trans*-4-amino-αβ-diethyl-4′-hydroxystilbene (Weiss, *J. Amer. Chem. Soc.*, 1949, **71**, 2944), m. p. 180—183°, raised the m. p. to 160—163°, thus suggesting that the crystals consist of a mixture of the *cis*- and the *trans*-form. However, shortage of material precluded any further work on their separation.

Reaction of 4-Acetamido-4′-acetoxy-α-ethyldeoxybenzoin with Ethylmagnesium Bromide.—The acetamido-compound (6·6 g.), dissolved in anisole (70 c.c.), was added during ½ hour to a mechanically stirred solution of ethylmagnesium bromide, prepared from magnesium (2·4 g., 5 equivs.), ethyl bromide (12 g.), and anhydrous ether (30 c.c.). The mixture was stirred at 25° for 2 hours and set aside overnight. The complex was decomposed with ammonium chloride solution and the ether–anisole layer was extracted with 2N-sodium hydroxide. Acidification of the alkaline extract with acetic acid yielded a gummy solid, which distilled at 245—250° (bath-temp.)/0·05 mm. The distillate deposited crystals, m. p. 194—197°, on treatment with ether. After recrystallisation from the methanol, these formed colourless needles, m. p. 200—201°, of 4-p-*acetamidophenyl*-3-p-*hydroxyphenylhexan*-3-*ol* (Found : C, 73·4; H, 7·65. $C_{26}H_{29}O_3N$ requires C, 73·4; H, 7·3%). Admixture with *trans*-4-amino-αβ-diethyl-4′-hydroxystilbene, m. p. 180—183°, produced a depression of 17°.

A second experiment, in which the diacetyl compound (12 g.) in anisole (120 c.c.) was treated with ethylmagnesium iodide [from magnesium (4·25 g.), ethyl iodide (27·6 g.), and anhydrous ether (75 c.c.)] at 50°, gave a gum which distilled at 231—237°/0·1 mm. The pale yellow glass obtained (4·7 g.) partly crystallised on treatment with ether, and crystallisation from methanol gave colourless crystals of 4-p-*aminophenyl*-3-p-*hydroxyphenylhexan*-3-*ol* (2·48 g.), m. p. 174—176°, raised to 181—182° by repeated recrystallisation from the same solvent (Found : C, 76·0; H, 7·7; N, 4·8. $C_{18}H_{23}O_2N$ requires C, 75·8; H, 8·1; N, 4·9%). Admixture with either *trans*-4-amino-αβ-diethyl-4′-hydroxystilbene (m. p. 180—183°) or 4-*p*-acetamidophenyl-3-*p*-hydroxyphenylhexan-3-ol produced a depression. 50 Mg. were treated in pyridine (1 c.c.) with *p*-nitrobenzoyl chloride (130 mg., 4 equivs.) at 20° for 1 hour, then 15 minutes at 60—70°. Water was added to precipitate the ON-*di*-p-*nitrobenzoyl* derivative (81 mg.), which was collected, washed with 0·1N-sodium carbonate and water, and dried at 80°. Crystallisation from methanol gave pale yellow prisms, m. p. 101—102° (Found : N, 7·1. $C_{32}H_{29}O_8N_3$ requires N, 7·2%).

αβ-Diethyl-4-methoxystilbene-4′-carbiminomethyl Ether (*Methyl αβ-Diethyl-4-methoxystilbene-4′-carboximidate*) *Hydrochloride.*—A mixture of 4-cyano-4′-methoxy-αβ-diethylstilbene (Neher and Miescher, *loc. cit.*) (1·93 g.) and anhydrous methanol (0·8 c.c.) was saturated at 0° with dry hydrogen chloride. The vessel was stoppered and set aside for 4 days, after which the excess of methanol and hydrogen chloride was removed under reduced pressure. The residue was dissolved in methanol and crystallisation was induced with ether. The *salt* (1·85 g., 77%) was obtained as a white crystalline powder, m. p. 160—162° (Found : N, 4·05; Cl, 10·1. $C_{21}H_{25}O_2N$,HCl requires N, 3·9; Cl, 9·9%).

4-Amidino-αβ-diethyl-4′-methoxystilbene Hydrochloride.—Finely powdered imino-ether hydrochloride (0·77 g.) was shaken mechanically with 10% alcoholic ammonia (4 c.c.) for 2 hours. The solid dissolved almost immediately, but the imino-ether base soon separated. This gradually redissolved during 48 hours. The mixture was evaporated under reduced pressure and crystallisation of the residue was induced with methanol and ether. Recrystallisation from water gave the required *amidine hydrochloride* as colourless needles, m. p. 202—203° (Found : C, 69·6; H, 7·25; N, 8·05; Cl, 10·2. $C_{20}H_{24}ON_2$,HCl requires C, 69·7; H, 7·25; N, 8·1; Cl, 10·3%).

3-p-*Methoxyphenyl*-4-p-*propionylphenylhexan*-3-*ol.*—A solution of 4-*p*-cyanophenyl-3-*p*-methoxyphenylhexan-3-ol (Jaeger and Robinson, *loc. cit.*) (5 g.) in anhydrous ether (25 c.c.) was added to a mechanically stirred, cooled solution of ethylmagnesium bromide, prepared from magnesium (2·5 g.), ethyl bromide (10·6 g.), and anhydrous ether (100 c.c.). The mixture was heated under reflux for 8 hours and set aside overnight. Decomposition was effected with acetic acid (30 c.c.) and water (20 c.c.), the ether was removed by distillation, and the mixture heated on a water-bath for 2 hours. The crude product was extracted with ether and freed from solvent. The residue was mixed with Girard's reagent T (4·5 g.), alcohol (45 c.c.), and acetic acid (4·5 c.c.) and heated under reflux for 1 hour. 3-p-*Methoxyphenyl*-4-p-*propionylphenylhexan*-3-*ol* was isolated by the procedure described by Jaeger and Robinson for 4 acetyl-αβ-diethyl-4′-methoxystilbene. It distilled at 220—230° (air-bath)/0·01 mm. as a pale yellow oil (2·46 g., 49%) (Found : C, 77·3; H, 8·15. $C_{22}H_{28}O_3$ requires C, 77·6; H, 8·2%).

αβ-Diethyl-4-methoxy-4′-propionylstilbene.—The above hexanol (3·15 g.) was heated with iodine (0·2 g.) and xylene (20 c.c.). Part of the solvent was slowly distilled to remove the water formed during

dehydration. The cooled solution was shaken with a solution of sodium thiosulphate to remove iodine, and dried (Na_2SO_4). The solvent was removed, and the residue distilled at 176—178°/0·06 mm. The *product* (2·7 g.) was a pale yellow oil (Found: C, 81·9; H, 7·9. $C_{22}H_{34}O_3$ requires C, 82·1; H, 8·1%).

Demethylation by boiling with hydriodic acid failed, only a trace of alkali-soluble material being formed. Most of the methoxy-derivative was recovered unchanged.

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161. *Lanosterol. Part X. Ketodihydrolanosterol (continued).*

By J. F. Cavalla and J. F. McGhie.

Oxidation of γ-lanostadienyl acetate with chromic acid gave keto-lanostenyl acetate, identical with that from lanostenyl acetate. This product was dehydrogenated by selenium dioxide to ketolanostatrienyl acetate which has also been isolated from the mother-liquors obtained in the preparation of γ-lanostadienyl acetate from lanostenyl acetate with selenium dioxide. Oxidation of the triene gave triketolanostadienyl acetate, the presence of an α-diketo-grouping in which was shown by oxidation with alkaline hydrogen peroxide to a dibasic acid. Ketolanostenyl acetate has been reduced to γ-lanostadienyl acetate.

Marker, Wittle, and Mixon (*J. Amer. Chem. Soc.*, 1937, **59**, 1368) reported that oxidation of lanostenyl acetate with chromic acid under comparatively mild conditions gave rise to two isomeric monoketolanostenyl acetates, designated by the prefixes α and β. Subsequent work (Birchenough and McGhie, *J.*, 1950, 1249) showed that only the β-isomer was a true keto-acetate, the supposed α-compound being impure γ-lanostadienyl acetate.* The isolation of only one keto-acetate is in conformity with the results of Ruzicka *et al.* (*Helv. Chim. Acta*, 1944, **27**, 472) who were also unable to obtain evidence for the formation of more than one ketolanostenyl acetate in the chromic acid oxidation of lanostenyl acetate.

Birchenough and McGhie (*loc. cit.*) also reported that under the conditions used by Marker *et al.* for the oxidation of lanostenyl acetate to ketolanostenyl acetate, γ-lanostadienyl acetate is rapidly oxidised to diketolanostenyl acetate; we have found that ketolanostenyl acetate behaves similarly.

γ-Lanostadienyl acetate on oxidation with perbenzoic acid or with ozone is readily converted into ketolanostenyl acetate (Birchenough and McGhie, *loc. cit.*; Birchenough, Thesis, London, 1950). We have now found it possible to oxidise γ-lanostadienyl acetate to ketolanostenyl acetate, in 20% yield, with chromic acid, using only one equivalent of oxidant and a short reaction time. This procedure is the most convenient for the rapid preparation of ketolanostenyl acetate. The identity of this product with that obtained by Ruzicka *et al.* or Birchenough and McGhie (*locc. cit.*) followed from physical properties and by dehydrogenation with selenium dioxide to the same ketolanostatrienyl acetate. Birchenough and McGhie (*loc. cit.*) showed that this compound was in all probability identical with a substance isolated by Muhr (Thesis, Zurich, 1945) from the mother-liquors left after the removal of γ-lanostadienyl acetate from the selenium dioxide oxidation of lanostenyl acetate. Although Muhr had formulated his compound as an unsaturated diketo-alcohol $C_{30}H_{44}O_3$, or less probably $C_{30}H_{46}O_3$, it being tentatively suggested that in the course of chromatographic purification deacetylation had occurred, all attempts to form an acetate failed. We have isolated Muhr's compound from the mother-liquors remaining after the conversion of lanostenyl acetate into γ-lanostadienyl acetate by selenium dioxide. It was identical with the ketolanostatrienyl acetate obtained from ketolanostenyl acetate according to Birchenough and McGhie (*loc. cit.*), and both were

* We revert to the nomenclature first used by Petrow (Thesis, London, 1935) in describing compounds obtained in reactions on lanosterol (now lanostadienol) derivatives.

oxidised by chromic acid to triketolanostadienyl acetate, m. p. 189—190°, $[\alpha]_D^{20}$ −60° (Dorée, McGhie, and Kurzer, *J.*, 1949, 570).

Recently Ruzicka and his collaborators (*Helv. Chim. Acta*, 1950, **33**, 1893) have reported failure to obtain consistent yields of triketolanostadienyl acetate following the directions of Dorée, McGhie, and Kurzer (*loc. cit.*) : the main product was reported to be a diketolanostadienyl acetate, m. p. 122°, $[\alpha]_D$ +77°, which on further treatment with selenium dioxide in dioxan at 180° was converted into triketolanostadienyl acetate identical with that obtained by Dorée *et al.*, although formulated as containing an additional double bond. We have, however, always obtained consistent yields of 30—35% of the triketoacetate, but no indication of the existence of an intermediate form as reported by Ruzicka *et al.* From our results, it appears that the controlling factor is the quantity of water used to dissolve the selenium dioxide. Dorée, McGhie, and Kurzer on the one hand state " a saturated aqueous solution," whilst Ruzicka *et al.* specify the amount of water used as 8 ml./3 g. of selenium dioxide. We have found that under anhydrous conditions (see McGhie, Thesis, London, 1947) consistent yields of triketolanostadienyl acetate (30%) can be obtained, even at the expense of cutting down the amounts of acetic anhydride used. However, we have found that as the amount of water used to dissolve the selenium dioxide increased, so the yields of the triketoacetate decreased and the quantity of diketolanostadienyl acetate increased until in the conditions used by Ruzicka it becomes the main product. In repeating this work we have isolated a product which appears to be identical with diketolanostadienyl acetate, having m. p. 128·5—129·5°, $[\alpha]_D$ 74·9°.

The triketo-acetate had the properties described by Dorée *et al.*, giving no colour with ferric chloride and failing to react with *o*-phenylenediamine even under forcing conditions. The presence of an α-diketo-grouping postulated by McGhie (*loc. cit.*) has been confirmed by oxidation with alkaline hydrogen peroxide in dioxan to an acid, m. p. 244°, $[\alpha]_D^{20}$ −57·5°, which gave analytical figures for a hydroxy-dibasic acid formed by simultaneous oxidation and hydrolysis.

Marker *et al.* first reported the conversion of lanostenyl acetate into γ-lanostadienyl acetate. Their method involved oxidation to ketolanostenyl acetate, followed by reduction to the diol with sodium and *iso*propyl alcohol and subsequent dehydration and acetylation with acetic anhydride. Since Birchenough and McGhie (*loc. cit.*) have already shown that only one of the two keto-acetates isolated by Marker was a true ketolanostenyl acetate, it was uncertain which of the two " isomers " was converted into γ-lanostadienyl acetate. Reduction of ketolanostenyl acetate (Birchenough and McGhie, *loc. cit.*) by Marker's method, followed by crystallisation, gave a product, the melting point of which slowly rose on repeated crystallisation to 156·5—157·5° (Marker *et al.* give m. p. 165°). Our product was identical with γ-lanostadienol, m. p. 157—158°. It is possible that during the purification continuous dehydration of the intermediate allylic alcohol takes place. All attempts to isolate the intermediate diol in a pure state by chromatography failed, even when the reduction was carried out with lithium aluminium hydride. Direct treatment of the reduction product with acetic anhydride gave γ-lanostadienyl acetate.

Experimental.

All m. p.s are uncorrected. Specific rotations were measured in chloroform solution at 20°. Aluminium oxide used in chromatographic work was from Messrs. Peter Spence Ltd. (Grade " 0 "). All analyses are by Drs. Weiler and Strauss, Oxford.

Ketolanostenyl Acetate.—γ-Lanostadienyl acetate (3 g.) in glacial acetic acid (100 ml.) was treated at 95° with a solution of chromic acid (0·75 g.) in 90% acetic acid (7·5 ml.) for 2 minutes, whereafter the mixture was quickly poured into water and the excess of chromic acid destroyed with dilute sulphurous acid, and the precipitated solid was taken up in ether. The ethereal solution was washed with water, then dilute sodium carbonate solution and water until neutral, and dried (Na_2SO_4), and the solvent removed to leave a light yellow solid. Crystallisation from ethyl acetate (12 ml.) gave impure ketolanostenyl (0·9 g.), m. p. 140—143° ; this was adsorbed from light petroleum (b. p. 60—80° ; 150 ml.) on a column of alumina (12 × 1·3 cm.). Elution with light petroleum (b. p. 60—80°)–benzene (1 : 1 ; 300 ml.) and benzene (300 ml.) gave, after crystallisation from acetone–methanol, glistening needles (0·6 g.) of ketolanostenyl acetate, m. p. 152—153°, $[\alpha]_D^{20}$ +18·5° (*c*, 0·040) (Found : C, 79·2; H, 10·9. Calc. for $C_{32}H_{52}O_2$: C, 79·3; H, 10·8%). Ultra-violet absorption spectrum : Max., 246 mμ. ; log ε, 4·06 in *cyclo*hexane; corresponding to $\lambda_{max.}$ 257 mμ. in alcohol. Authentic material is stated to have m. p. 151—152·5°, $[\alpha]_D^{19}$ +21·3°, and $\lambda_{max.}$ 255 mμ. (log ε 4·08) in alcohol. From the ethyl acetate mother-liquors, diketolanostenyl acetate was obtained.

Ketolanostatrienyl Acetate.—Ketolanostenyl acetate (4 g.) in glacial acetic acid (100 ml.) was refluxed for 3 hours with a solution of selenium dioxide (2 g.) in water (2 ml.). The product was worked up by Birchenough and McGhie's method (*J.*, 1950, 1249), yielding pure ketolanostatrienyl acetate (2·8 g.), m. p. 198—199°, $[\alpha]_D^{20}$ +70·2° (*c*, 0·046) (Found : C, 80·0; H, 10·2. Calc. for $C_{32}H_{48}O_2$: C, 80·0; H, 10·1%). Absorption : Max., 256 and 328 mμ. ; log ε, 3·89 in alcohol.

Examination of the Mother-liquors remaining from the Oxidation of Lanostenyl Acetate to γ-Lanostadienyl Acetate (Dihydroagnosteryl Acetate).—The mother-liquors (3 l.) corresponding to the oxidation of approx. 200 g. of lanostenyl acetate were evaporated in a vacuum to 100 ml. and then poured into water. The precipitated solids were extracted with ether, and the ethereal layer was washed with water and sodium carbonate solution until neutral. Removal of the ether gave a red solid. Passage of its deep-red solution in benzene through alumina (25 × 4 cm.) removed most of the colloidal selenium, leaving a light brown solid on removal of the solvent. Crystallisation from acetone–methanol gave an ill-formed product (3 g.), m. p. 140—150°, which was dissolved in light petroleum (b. p. 60—80°) (150 ml.) and adsorbed on alumina (15 × 1·3 cm.). Elution with light petroleum (b. p. 60—80°; 500 ml.) gave γ-lanostadienyl acetate, m. p. 168—169° (0·5 g.); benzene (500 ml.) eluted ketolanostatrienyl acetate (1·3 g.), m. p. 196—199°, one crystallisation from ethyl acetate–methanol giving the pure compound, m. p. 198—199°, $[\alpha]_D^{20}$ +68·9° (*c*, 0·081) (Found: C, 80·1; H, 10·1%). Absorption: Max., 256 and 328 mμ.; log ε, 3·89 in alcohol. A mixed m. p. with authentic material gave m. p. 198—199°.

Triketolanostadienyl Acetate.—Ketolanostatrienyl acetate (0·65 g.) in glacial acetic acid (50 ml.) was treated at 95° for 1 hour with chromic acid (0·65 g.) in 90% acetic acid (6·5 ml.) and then poured into water; the excess of chromic acid was destroyed with dilute sulphurous acid. The precipitated solids were extracted with ether, the ethereal layer was washed with water and dilute sodium carbonate solution until neutral, then dried (Na_2SO_4), and the solvent removed. The residual orange solid was crystallised from methanol (20 ml.), giving fine orange needles (0·45 g.), m. p. 186—188°. Two further recrystallisations gave pure triketolanostadienyl acetate, m. p. 189—190°, $[\alpha]_D^{20}$ −60·0° (*c*, 0·033) (Found: C, 75·2; H, 9·2. Calc. for $C_{32}H_{44}O_5$: C, 75·3; H, 9·1%). Absorption: Max., 284 mμ.; log ε, 4·01 in alcohol.

A similar experiment with ketolanostatrienyl acetate obtained from the mother-liquors from γ-lanostadienyl acetate gave triketolanostadienyl acetate, m. p. 189—190°, alone and on admixture with an authentic specimen.

Dorée, McGhie, and Kurzer (*J.*, 1949, 570), and Voser *et al.* (*Helv. Chim. Acta*, 1950, **33**, 1893) respectively report m. p. 184—187°, 189—190°, $[\alpha]_D$ −50·4°, −61° to −63°, $\lambda_{max.}$ 280 (log ε 4·10), 285 (log ε 4·0) in alcohol.

Treatment of Diketolanostenyl Acetate with Selenium Dioxide.—(a) *Conditions described by Ruzicka* et al. (loc. cit.). Diketolanostenyl acetate (3 g.) dissolved in glacial acetic acid–acetic anhydride (50 ml.; 1 : 1) was refluxed for 3½ hours with a solution of selenium dioxide (3 g.) in water (8 ml.). Chromatographic purification of the product gave lemon-yellow needles (1·3 g.), m. p. 128·5—129·5°, $[\alpha]_D^{20}$ +74·9° (*c*, 0·038) (Found: C, 77·2; H, 9·6. Calc. for $C_{32}H_{46}O_4$: C, 77·4; H, 9·7%), as described by Ruzicka *et al.* A mixed m. p. of this compound with the starting material was 128—140°. From the benzene chromatographic eluates, triketolanostadienyl acetate, m. p. 188—189°, was obtained in small yield.

(b) *Anhydrous conditions.* Diketolanostenyl acetate (3 g.) was added to a suspension of selenium dioxide (3 g.) in acetic acid–acetic anhydride (50 ml.; 1 : 1) and refluxed for 3½ hours. The precipitated black selenium was filtered off and the filtrate poured into water. Extraction with ether and removal of solvent gave a red solid, crystallising from acetone–methanol in red needles (1·5 g.), m. p. 170—176°. Adsorption of this product on alumina (15 × 1·3 cm.) from light petroleum (b. p. 60—80°; 100 ml.) gave the following fractions on elution: (*a*) light petroleum (b. p. 60—80°; 400 ml.), trace of oil; (*b*) light petroleum (b. p. 60—80°)–benzene (2 : 1; 300 ml.), 0·15 g. of yellow oil; (*c*) light petroleum (b. p. 60—80°)–benzene (1 : 2; 300 ml.), 0·2 g. of orange solid; (*d*) benzene (300 ml.), 0·9 g. of orange solid; (*e*) chloroform (300 ml.), 0·1 g. of orange solid. Fraction (*b*), crystallised from methanol, gave diketolanostadienyl acetate as lemon-yellow needles, m. p. 127—128°, brought by two recrystallisations from methanol to m. p. 128·5—129·5° alone or on admixture with material prepared as above. Fraction (*c*), crystallised from methanol, gave slightly impure triketolanostadienyl acetate, m. p. 184—185°. Fractions (*d*) and (*e*) crystallised from acetone–methanol to give triketolanostadienyl acetate as fine orange needles, m. p. 188—190°, brought by one crystallisation to m. p. 189—190°, $[\alpha]_D^{20}$ −60·5° (*c*, 0·062) (Found: C, 75·2; H, 9·2. Calc. for $C_{32}H_{44}O_5$: C, 75·3; H, 9·1%).

Treatment of Triketolanostadienyl Acetate with Hydrogen Peroxide.—To a solution of triketolanostadienyl acetate (0·45 g.) in dioxan (25 ml.) was added aqueous potassium hydroxide (8 ml.; 10%) and then, at 50°, "Perhydrol" (4 ml.). The colour of the solution faded and after 15 minutes was almost nil. A further ml. of "Perhydrol" was added and the solution left for 10 minutes, poured into water, and extracted with ether. The ethereal layer was further extracted with 10% aqueous potassium hydroxide, then washed with water, and the solvent removed to leave a negligible neutral fraction. Acidification of the alkaline fraction gave a white solid which, on extraction with ether and crystallisation from ethyl acetate, gave cubic crystals (0·3 g.), m. p. 244° (decomp.), $[\alpha]_D^{20}$ −57·5° (*c*, 0·022 in alcohol). This was a *hydroxy-dibasic acid* (Found: C, 71·5, 71·4; H, 9·2, 9·0. $C_{36}H_{44}O_6$ requires C, 71·7; H, 9·2%). Absorption: Max., 251 mμ.; log ε, 4·03 in alcohol.

Reduction of Ketolanostenyl Acetate.—(a) *Sodium and isopropyl alcohol.* Sodium (3 g.) was added slowly during 1 hour to a refluxing solution of ketolanostenyl acetate (0·5 g.) in dry *iso*propyl alcohol (50 ml.). The solution was boiled for a further 2 hours and then poured into water. Extraction with ether, followed by crystallisation from methanol–acetone, gave felted white needles (0·33 g.), m. p. 140—146°. Recrystallisation of this product six times from the same solvents raised the m. p. to a constant value of 156·5—157·5°, undepressed on admixture with an authentic specimen of γ-lanostadienol, m. p. 157—158°. Concentration of the mother-liquors from this purification to 30 ml. gave felted needles (0·1 g.), m. p. 128—130°. Further concentration of the mother-liquor gave a semicrystalline material (0·08 g.), m. p. 196—202°, which by repeated crystallisation from aqueous methanol gave fine needles of a *diol*, m. p. 207—208° (Found: C, 81·0; H, 11·9. $C_{30}H_{52}O_2$ requires C, 81·0; H, 11·8%).

(b) *Lithium aluminium hydride.* A solution of ketolanostenyl acetate (0·5 g.) in absolute ether (50 ml.) was added dropwise to a suspension of lithium aluminium hydride (1·3 g.) in abolute ether (100 ml.), with mechanical stirring and under reflux. A white solid was precipitated and the ether boiled gently. Stirring was continued for 1 hour, and the excess of lithium aluminium hydride then decomposed by cautious addition of ice-water, followed by dilute sulphuric acid. Extraction of the mixture with ether gave, on removal of the solvent, a colourless solid which was adsorbed from light petroleum (b. p. 60—80°; 250 ml.) on a column of alumina (12 × 1·3 cm.). Elution with light petroleum (b. p. 60—80°)–benzene (1 : 1; 500 ml.) and benzene (500 ml.) gave a white solid (0·35 g.), crystallising from acetone–methanol in felted needles, m. p. 153—155°. Three recrystallisations from the same mixture gave felted needles of γ-lanostadienol, m. p. 156—157°, $[\alpha]_D^{20}$ 67·8° (*c*, 0·057), undepressed on admixture with authentic material (Found: C, 84·9; H, 11·7. Calc. for $C_{30}H_{50}O$: C, 84·4; H, 11·8%).

Acetylation. The crude products from both the above reductions were severally boiled with acetic anhydride (25 ml.) for 2 hours. Pouring into water and extraction with ether in the usual manner gave a white solid which crystallised from acetone–methanol in glistening plates, m. p. 167—168°, in each case, undepressed on admixture with authentic γ-lanostadienyl acetate, $[\alpha]_D^{20}$ 91·0° (*c*, 0·033) (Found: C, 82·1; H, 11·0. Calc. for $C_{32}H_{52}O_2$: C, 82·0; H, 11·2%). Absorption: Max. 244 ($E_{1\,cm.}^{1\%}$ 360) and 251 mμ. ($E_{1\,cm.}^{1\%}$ 224).

Diketolanostenyl Acetate.—Ketolanostenyl acetate (0·5 g.), in glacial acetic acid (50 ml.) was treated at 90° with a solution of chromic acid (0·5 g.) in 90% acetic acid (5 ml.) for 1 hour, with mechanical stirring, and then poured into water; the excess of chromic acid was then destroyed with dilute sulphurous acid. Extraction of the precipitated solids with ether in the usual manner and removal of the solvent gave a yellow solid crystallising from methanol in glistening yellow plates (0·35 g.), m. p. 155—157°. Two recrystallisations from methanol gave diketolanostenyl acetate, m. p. 157—158° (undepressed on admixture with authentic material), $[\alpha]_D^{20}$ +91·6° (*c*, 0·024) (Found: C, 77·1; H, 10·1. Calc. for $C_{32}H_{50}O_4$: C, 77·1; H, 10·1%).

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CHELSEA POLYTECHNIC, MANRESA ROAD, S.W.3. [*Received, November 30th*, 1950.]

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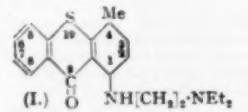
162. *Xanthones and Thioxanthones. Part I. The Synthesis of 2- and 3-Dialkylaminoalkylamino-derivatives.*

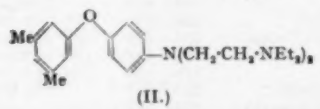
By FREDERICK G. MANN and J. HEDLEY TURNBULL.

A number of 2- and 3-dialkylaminoalkylamino-xanthones and -thioxanthones, with and without other nuclear substituents, have been synthesised and their value as possible drugs for the treatment of schistosomiasis and amœbiasis has been assayed. Although several showed amœbicidal activity *in vitro*, none showed significant activity towards schistosomiasis infections in mice.

A CONSIDERABLE number of xanthones and thioxanthones having the diethylaminoethylamino-group in the 1 or the 4-position have been prepared by Mauss (*Chem. Ber.*, 1948, **81**, 19) and tested as possible drugs for treatment of schistosomiasis. The most effective of these compounds is 1-2′-diethylaminoethylamino-4-methylthioxanthone (I), known as "Miracil-D."

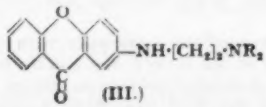


(I.)

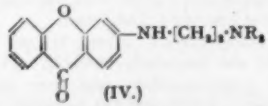


(II.)

In the diphenyl ether series, however, it is known that *p*-di-(2-diethylaminoethyl)aminophenyl *m*-5-xylyl ether (II), known as Gavano base, has considerable activity against amœbiasis.



(III.)

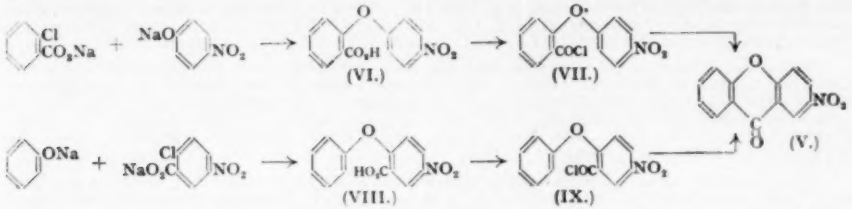


(IV.)

In general, type (I) and (II) are clearly not widely dissimilar, and we have therefore investigated in particular the synthesis of various xanthones and thioxanthones having basic

side chains in the 2 or the 3 position, in view of the fact that Mauss's work was limited to the more readily accessible derivatives having these groups in the 1 or the 4 position.

The synthesis of 2-(2-dialkylaminoethylamino)xanthones (III) and of the 3-substituted analogues (IV) involved in each case the preparation of the corresponding 2- and 3-nitroxanthones. 2-Nitroxanthone (V) was initially prepared by a modification of Dhar's method (*J.*, 1920, **117**, 1057), sodium *o*-chlorobenzoate and sodium *p*-nitrophenoxide condensing to



give *o*-carboxyphenyl *p*-nitrophenyl ether (VI), which was then converted into the chloride (VII); the latter on treatment with aluminium chloride underwent cyclisation to (V). In a second method, which afforded larger yields, sodium phenoxide and sodium 2-chloro-5-nitrobenzoate were condensed to give 2-carboxy-4-nitrophenyl phenyl ether (VIII), which was similarly converted into the chloride (IX) and then cyclised to (V). The use of the sodium derivatives of *p*-chlorophenol and of *m*-5-xylenol in this second method similarly gave 7-chloro-2-nitroxanthone and 6 : 8-dimethyl-2-nitroxanthone.

When this method was similarly applied to the condensation of sodium phenoxide and sodium 2-chloro-4-nitrobenzoate 3-nitroxanthone (Ullmann and Wagner, *Annalen*, 1907, **355**, 362) was obtained.

The nitroxanthones were then reduced to the aminoxanthones by stannous chloride, which left the carbonyl group unchanged. The aminoxanthones were crystalline, feebly basic compounds, and their hydrochlorides were readily hydrolysed by water. The 2-aminoxanthones were yellow and the 3-aminoxanthones colourless; both series dissolved in sulphuric acid to give a blue fluorescence (cf. Purgotti, *Gazzetta*, 1914, **44**, 644; Ullmann and Wagner, *loc. cit.*).

The aminoxanthones readily condensed with 2-diethylaminoethyl chloride to give the corresponding diethylaminoethylaminoxanthones (III and IV). In the case of 2-amino-7-chloroxanthone the corresponding 7-chloro-2-(2-di-*n*-butylaminoethylamino)xanthone was similarly prepared in order to determine the therapeutic effect of increasing the carbon chain of the terminal alkyl groups.

The substituted xanthones thus obtained are listed, with their melting points, in Table I. The 2-dialkylaminoalkylamino-derivatives were yellow crystalline solids, whereas the 3-substituted analogues were colourless. Certain physical and chemical properties were clearly parallel to those of the corresponding thioxanthones which are discussed in greater detail later.

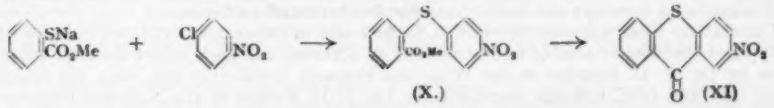
TABLE I.

Xanthone.	M. p.	Xanthone.	M. p.
2-Nitro-	203—204°	3-Amino-	228—230°
7-Chloro-2-nitro-	254—255	(i) 2-(2-Diethylaminoethylamino)-	79—81
6 : 8-Dimethyl-2-nitro-	222—223	(ii) 7-Chloro-2-(2-diethylaminoethylamino)-	124—126
3-Nitro-	173—175	(iii) 7-Chloro-2-(2-di-*n*-butylaminoethylamino)-	105—106
2-Amino-	210—212	(iv) 2-(2-Diethylaminoethylamino)-6 : 8-dimethyl-	85—87
2-Amino-7-chloro-	231—232	3-(2-Diethylaminoethylamino)-	87—89
2-Amino-6 : 8-dimethyl-	209—210		

In addition to the above compounds, it was clearly desirable to investigate another series carrying the di-(2-diethylaminoethyl)amino-side-chain present in (II). All attempts to condense 2-iodoxanthone with di-(2-diethylaminoethyl)amine, failed, however, and further work on these lines has been postponed.

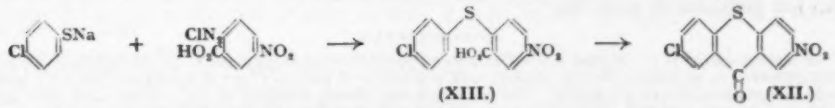
In the thioxanthone series, the most important intermediate compounds were again the 2-nitro- and the 3-nitro-derivatives. For the synthesis of the former, the sodium derivative of methyl *o*-mercaptobenzoate was condensed with *p*-chloronitrobenzene giving *o*-carbomethoxyphenyl *p*-nitrophenyl sulphide (X). This ester was then hydrolysed and converted into the carboxychloride, and the latter cyclised with aluminium chloride to the 2-nitrothioxanthone (XI) (cf. Mayer, *Ber.*, 1909, **42**, 3046). This method was also used for the prepar-

ation of 7-methyl-, 6 : 8-dimethyl-, and 7-chloro-2-nitrothioxanthone (XII), although the last of these compounds was obtained only in low yield.



(X.) (XI)

For the preparation of the 7-chloro-compound (XII) in reasonable yield however, a second (but similar) synthesis was employed. Sodium *p*-chlorothiophenoxide was brought into reaction with diazotised 5-nitroanthranilic acid whereby 2-carboxy-4-nitrophenyl *p*-chlorophenyl sulphide (XIII) was obtained, and then by the usual stages converted into (XII).



(XIII.) (XII.)

The latter synthesis, diazotised 4-nitroanthranilic acid being used however, was employed to prepare 3-nitrothioxanthone (Mayer, *loc. cit.*) and also, by the use of the appropriately substituted thiophenols, to prepare 7-chloro-3-nitro- and 7-methyl-3-nitro-thioxanthone.

The nitrothioxanthones were reduced as before by stannous chloride to the aminothioxanthones. It is noteworthy that the 2-amino-compounds were orange and the 3-amino-analogues pale yellow. Both series dissolved in sulphuric acid to give a green fluorescence. In both the xanthone and the thioxanthone series, therefore, the 2-amino-derivatives were darker than the 3-amino-analogues.

(XIV.) (XV.)

Condensation of these amino-derivatives with 2-diethylaminoethyl chloride as before gave the 2- and 3-diethylaminoethylaminothioxanthones (XIV and XV; R = Et). As in the xanthone series, the 7-chloro-2-(2-di-*n*-butylaminoethylamino)-compound was also prepared. The compounds thus obtained, and the intermediate compounds required, are listed in Table II.

TABLE II.

Thioxanthone.	M. p.	Thioxanthone.	M. p.
2-Nitro-	224—225°	3-Amino-	252—254°
7-Chloro-2-nitro-	271—272	3-Amino-7-chloro-	278—279
7-Methyl-2-nitro-	257—260	3-Amino-7-methyl-	234—236
6 : 8-Dimethyl-2-nitro-	225—226	(v) 2-(2-Diethylaminoethylamino)-	52—53
3-Nitro-	252	(vi) 7-Chloro-2-(2-diethylaminoethylamino)-	128—129
7-Chloro-3-nitro-	322—323	(vii) 7-Chloro-2-(2-di-*n*-butylaminoethylamino)-	104—105
7-Methyl-3-nitro-	274—275	(viii) 2-(2-Diethylaminoethylamino)-7-methyl-	73—75
2-Amino-	227—228	(ix) 3-(2-Diethylaminoethylamino)-	91—92
2-Amino-7-chloro-	228—230	(x) 7-Chloro-3-(2-diethylaminoethylamino)-	112—113
2-Amino-7-methyl-	194—195	(xi) 3-(2-Diethylaminoethylamino)-7-methyl-	81—83

Certain properties of the final products merit brief discussion. The orange-red 2-dialkylaminoethylamino-compounds (XIV) readily formed stable dihydrochlorides, whereas the pale-yellow 3-substituted isomers (XV) formed poorly crystalline dihydrochlorides which readily dissociated to the monohydrochlorides in the presence of water; both series of compounds formed highly crystalline mono-3 : 5-dinitrobenzoates, which were excellent for characterisation. Furthermore, both series, when treated with a solution of zinc chloride in hydrochloric acid, readily gave crystalline chlorozincates, $C_6H_4\langle^{S}_{CO}\rangle C_6H_3{\cdot}NH[CH_2]_2{\cdot}NEt_2,H_2ZnCl_4$. These chlorozincates in the 2-substituted series formed white needles which crystallised unchanged from hydrochloric acid, but dissolved in water to give orange-yellow solutions. In the 3-substituted series, however, the chlorozincates formed brilliant orange plates, which were

easily hydrolysed even in dilute hydrochloric acid solution but dissolved in water to colourless solutions. The colours of the chlorozincates of the two series are thus the reverse of those of the monoamino-compounds and of the diamino-compounds (XIV and XV), in which the 2-substituted members are darker than the 3-substituted analogues.

The activity of compounds (i)—(iv) in Table I and of compounds (v)—(xi) in Table II, in the form of their water-soluble hydrochlorides or acetates, has been tested towards schistosomiasis by Dr. O. D. Standen at the Wellcome Research Institution and, with the exception of (ii), (iii), and (vii), towards amœbiasis by Dr. J. D. Fulton at the National Institute for Medical Research. The compounds proved inactive towards *Schistosoma mansoni* infections in mice, but all those tested showed amœbicidal activity *in vitro*. Compound (vi) was most promising as an amœbicidal agent, and was lethal to *E. histolytica* in dilutions of 1 : 100,000; this can be compared with Gavanò base (II) which under comparable conditions was lethal at a dilution of 1 : 1,000,000. It is noteworthy that the compounds (i), (v), (vi), (ix), (x), and (xi) had antibacterial properties.

Experimental.

2-Nitroxanthone (V). *Method* 1.—*o-Carbomethoxyphenyl p-nitrophenyl ether.* *p*-Nitrophenol (42 g.) was dissolved in methanol (50 c.c.), mixed with a solution of sodium (7 g.) in methanol (100 c.c.), and *o*-chlorobenzoic acid (47 g.) added. The methanol was slowly distilled off on a steam-bath and the temperature raised to 160—165° for 1 hour. After a further hour at 160—165° the product was dissolved in methanol (250 c.c.), boiled under reflux for 3 hours in a stream of dry hydrogen chloride, and poured on ice, and the oil extracted with ether. The extracts were shaken with excess of ice-cold dilute sodium hydroxide solution, filtered, washed free from sodium *p*-nitrophenoxide, and then steam-distilled. The residual oily product crystallised on cooling, to give the *methyl* ester, which separated from methanol in large crystals (13 g.), m. p. 76—78° (Found: C, 61·9; H, 4·3; N, 5·1. $C_{14}H_{11}O_5N$ requires C, 61·5; H, 4·05; N, 5·15%).

o-Carboxyphenyl p-nitrophenyl ether (VI). The foregoing ester (0·6 g.) was hydrolysed by heating it under reflux with N-potassium hydroxide (10 c.c.) for 2 hours. The *carboxylic acid* separated from benzene in clusters of crystals (0·5 g.), m. p. 153—155° (Found: C, 60·3; H, 3·7; N, 5·2. $C_{13}H_9O_5N$ requires C, 60·2; H, 3·5; N, 5·4%).

The xanthone. A mixture of the acid (13 g.), benzene (130 c.c.), and thionyl chloride (13 c.c.) was heated on the water-bath for 2 hours. The benzene was removed, the residue dissolved in nitrobenzene (130 c.c.), and the solution cooled to 0° and dropped into a mixture of aluminium chloride (13 g.) and nitrobenzene (130 c.c.) with ice-cooling. The mixture was set aside overnight at 0°, ice was then added, and excess of nitrobenzene removed by steam-distillation. The residual solution was cooled, and the xanthone (9·7 g.), m. p. 200—202°, collected and recrystallised from glacial acetic acid, giving white crystals, m. p. 203—204° (Found: C, 64·8; H, 3·0; N, 5·8. Calc. for $C_{13}H_7O_4N$: C, 64·7; H, 2·95; N, 5·8%). Dhar (*loc. cit.*) records m. p. 200°.

2-Nitroxanthone (V). *Method* 2.—*2-Chloro-5-nitrobenzoic acid.* This was prepared by the nitration of *o*-chlorobenzoic acid (20 g.) (Rupe, *Ber.*, 1897, **30**, 1099), and after recrystallisation from water was obtained as glistening plates (14 g.), m. p. 161—163°.

2-Carbomethoxy-4-nitrophenyl phenyl ether. 2-Chloro-5-nitrobenzoic acid (17 g.) was added to a solution of sodium (3·9 g.) in methanol (80 c.c.), and the semi-solid product mixed with phenol (31·6 g.). The bulk of the methanol was distilled off and the temperature of the residue then raised to 175—189° during 30 minutes with occasional stirring; the mass melted and effervesced. As soon as the reaction had subsided, the product was steam-distilled to remove excess of phenol, and the residual solution acidified with hydrochloric acid. The precipitate was collected, dried (21·5 g.), dissolved in methanol (200 c.c.), heated under reflux in a stream of dry hydrogen chloride for 2 hours, and then poured on ice, whereupon the *ester* slowly crystallised: it (18·5 g.) had m. p. 80—82°, and recrystallised from methanol as white needles, m. p. 82° (Found: C, 61·8; H, 3·9; N, 5·0. $C_{14}H_{11}O_5N$ requires C, 61·5; H, 4·1; N, 5·1%).

2-Carboxy-4-nitrophenyl phenyl ether (VIII). This *acid* was prepared by heating the ester (17 g.) with N-potassium hydroxide solution (300 c.c.) under reflux, and was ultimately crystallised from ethanol–water (1 : 1 by volume), forming minute white needles (14 g.), m. p. 166—168° (Found: C, 60·3; H, 3·4; N, 5·2. $C_{13}H_9O_5N$ requires C, 60·2; H, 3·5; N, 5·4%).

The xanthone. The acid (13 g.), suspended in benzene (130 c.c.), was warmed on the water-bath with thionyl chloride (13 c.c.) for 4 hours. The solution was evaporated to dryness in a vacuum, and the residue dissolved in nitrobenzene (130 c.c.) and treated with aluminium chloride (13 g.) in the usual way, to give the nitroxanthone, m. p. 200—202°, (9·7 g.), which crystallised from glacial acetic acid in white crystals, m. p. 203°, identical with the material prepared by the first method.

7-Chloro-2-nitroxanthone.—2-Carbomethoxy-4-nitrophenyl p-chlorophenyl ether. 2-Chloro-5-nitrobenzoic acid (4·0 g.) was mixed with a solution of sodium (0·92 g.) in methanol (20 c.c.), and *p*-chlorophenol (10·3 g.) added. The condensation, carried out in the usual way, gave the crude acid, m. p. 160—175° (5·6 g.), which was converted into the *methyl* ester (5·0 g.), m. p. 160—162°. This ester was recrystallised from methanol, giving long white needles, m. p. 162° (Found: C, 54·6; H, 3·0; N, 4·7. $C_{14}H_{10}O_5NCl$ requires C, 54·6; H, 3·25; N, 4·55%).

2-Carboxy-4-nitrophenyl p-chlorophenyl ether. This acid was prepared by heating the ester (4·5 g.) under reflux with N-potassium hydroxide (100 c.c.) for 30 minutes, and was obtained as a solid (4·1 g.),

m. p. 177—179°, which separated from benzene as white crystals of the *ether*, m. p. 180—181° (Found : C, 52·9; H, 3·0; N, 5·1. $C_{13}H_8O_4NCl$ requires C, 53·2; H, 2·75; N, 4·8%).

The xanthone. The acid (3·6 g.), benzene (36 c.c.), and thionyl chloride (3·6 c.c.) were heated on the water-bath for 4 hours. The benzene was removed, and the residue cyclised by treatment with aluminium chloride (3·6 g.) in nitrobenzene to give the *nitroxanthone* (3·0 g.) which crystallised from glacial acetic acid in glistening plates, m. p. 254—255° (Found : C, 56·6; H, 2·6; N, 5·3. $C_{13}H_6O_4NCl$ requires C, 56·6; H, 2·2; N, 5·1%).

6 : 8-*Dimethyl-2-nitroxanthone.*—*2-Carbomethoxy-4-nitrophenyl* m-5-*xylyl ether.* 2-Chloro-5-nitrobenzoic acid (4 g.) was added to a solution of sodium (0·92 g.) in methanol (20 c.c.), and the reddish semi-solid product mixed with *m*-5-xylenol (9·8 g.). The condensation was carried out as already described, and gave the crude acid (5·4 g.), which was converted into the *methyl* ester, recrystallising from methanol, as glistening plates (4·5 g.), m. p. 83—85° (Found : C, 63·4; H, 4·65; N, 5·0. $C_{16}H_{15}O_5N$ requires C, 63·8; H, 5·0; N, 4·7%).

2-Carboxy-4-nitrophenyl m-5-*xylyl ether.* The ester (4·5 g.) was heated under reflux with N-potassium hydroxide (100 c.c.) for 1 hour. The acid crystallised from ethanol–water (1 : 1 by volume) as white needles (3·7 g.), m. p. 184—185° (Found : C, 62·5; H, 4·95; N, 5·1. $C_{15}H_{13}O_5N$ requires C, 62·7; H, 4·6; N, 4·9%).

The xanthone. This acid (14·1 g.), benzene (140 c.c.), and thionyl chloride (14 c.c.) were heated on a water-bath for 2 hours. The benzene was removed, and the residue dissolved in nitrobenzene (140 c.c.) and treated with aluminium chloride (14 g.), to give the *nitroxanthone* (12·4 g.), m. p. 217—219°, which crystallised from glacial acetic acid in needles, m. p. 222—223° (Found : C, 66·9; H, 3·7; N, 5·3. $C_{15}H_{11}O_4N$ requires C, 66·9; H, 4·1; N, 5·2%).

3-*Nitroxanthone.*—2-Chloro-4-nitrobenzoic acid (2 g.) (Ullmann and Wagner, *loc. cit.*) and phenol (4 g.) were added in turn to sodium (0·46 g.), dissolved in methanol (10 c.c.). The condensation was carried out in the usual way and the product (2·1 g.) was treated with thionyl chloride and cyclised in the presence of aluminium chloride to give 3-nitroxanthone (1·0 g.), m. p. 173—175°. Ullmann and Wagner record m. p. 176°.

2-*Aminoxanthone.*—2-Nitroxanthone (9·2 g.) was suspended in acetic acid (140 c.c.), stannous chloride (41 g.) in concentrated hydrochloric acid (57·5 c.c.) was added, and the mixture was heated for 3 hours at 100°. The solid was collected and digested with excess of hot 2·5N-sodium hydroxide, and the precipitate recrystallised from ethanol giving small bright-yellow needles (4·7 g.), m. p. 210—212° (Found : C, 74·0; H, 4·4; N, 6·9. Calc. for $C_{13}H_9O_2N$: C, 73·9; H, 4·3; N, 6·6%). Purgotti (*loc. cit.*) records m. p. 205°.

2-*Amino-7-chloroxanthone.*—7-Chloro-2-nitroxanthone (2·5 g.) was suspended in acetic acid (45 c.c.), stannous chloride (7·3 g.) in concentrated hydrochloric acid (11·5 c.c.) added, and the mixture warmed on the water-bath for 2 hours. The solid was collected, reduced again under the same conditions, and then shaken with 2·5N-sodium hydroxide (175 c.c.) for 2 hours, giving the *amine* which crystallised from ethanol in yellow needles (1·6 g.), m. p. 231—232° (Found : C, 63·4; H, 3·4; N, 5·95. $C_{13}H_8O_2NCl$ requires C, 63·6; H, 3·3; N, 5·7%).

2-*Amino*-6 : 8-*dimethylxanthone.*—This *amine* was obtained by the reduction of the nitro-compound precisely as described for the chloro-base, and after crystallisation from ethanol, furnished yellow needles, m. p. 209—210° (Found : C, 75·2; H, 5·6; N, 5·5. $C_{15}H_{13}O_2N$ requires C, 75·3; H, 5·5; N, 5·8%).

3-*Aminoxanthone.*—This was similarly prepared, and recrystallised from benzene in glistening plates, m. p. 228—230° (Found : C, 73·9; H, 4·5; N, 6·6. Calc. for $C_{13}H_9O_2N$: C, 73·9; H, 4·3; N, 6·6%). Ullmann and Wagner (*loc. cit.*) give m. p. 232°.

2-(2-*Diethylaminoethylamino*)*xanthone* (III; R = Et).—2-Aminoxanthone (1 g.) and 2-diethylaminoethyl chloride hydrochloride (0·9 g.) were intimately mixed and heated for 1 hour at 150—155°. The product was extracted with hot dilute acetic acid (60 c.c.), the extracts were filtered, and the filtrates basified with sodium hydroxide solution and steam-distilled. The residual suspension was extracted with ether, the ethereal extracts were shaken with 10% acetic acid, and the acid solution was basified with ammonia solution. The liberated *base*, isolated by extraction with ether, was obtained as a gum which crystallised from light petroleum (b. p. 40—60°) in glistening yellow plates (0·64 g.), m. p. 79—81° (Found : C, 73·3; H, 7·0; N, 9·1. $C_{19}H_{22}O_2N_2$ requires C, 73·5; H, 7·2; N, 9·05%).

The 3 : 5-*dinitrobenzoate* crystallised from methanol in bright-red plates, m. p. 179—181° (Found : C, 59·9; H, 4·9; N, 10·4. $C_{19}H_{22}O_2N_2.C_7H_4O_6N_2$ requires C, 59·8; H, 5·0; N, 10·7%).

The *dihydrochloride*, prepared by adding cold saturated ethanolic hydrogen chloride (30 c.c.) to a solution of the base (3·0 g.) in warm ethanol (150 c.c.), crystallised as small faintly-yellow plates (3·6 g.), m. p. 210° (decomp.) (sinters 205°) (Found : N, 7·2. $C_{19}H_{22}O_2N_2.2HCl$ requires N, 7·3%).

The *chlorozincate* separated when a warm concentrated alcoholic solution of the base was mixed with 2% zinc chloride–dilute hydrochloric acid reagent. It formed minute lustrous white plates, m. p. 255° (decomp.) (Found : C, 41·0; H, 5·0; N, 5·4. $C_{19}H_{22}O_2N_2.H_2ZnCl_4.2H_2O$ requires C, 41·1; H, 5·1; N, 5·0%). An aqueous solution of the salt was orange-yellow.

7-*Chloro*-2-(2-*diethylaminoethylamino*)*xanthone.*—2-Diethylaminoethyl chloride hydrochloride (1·8 g.) was shaken with cold aqueous potassium carbonate and xylene (35 c.c.). The xylene layer was separated, dried, mixed with 2-amino-7-chloroxanthone (0·7 g.) and anhydrous potassium carbonate (0·7 g.), and heated under reflux for 48 hours. The product was washed with dilute sodium hydroxide solution, then steam-distilled, and the residual suspension extracted with ether. The extracts were shaken with successive portions of 10% acetic acid, and the acid extracts made alkaline with ammonia

solution. The *base* (0·6 g.), isolated by extraction with ether, was obtained as a solid, m. p. 123—125°, which, when crystallised from light petroleum (b. p. 40—60°) and then from dilute ethanol, afforded yellow needles, m. p. 124—126° (Found: C, 66·4; H, 6·1; N, 8·3. $C_{19}H_{21}O_2N_2Cl$ requires C, 66·2; H, 6·1; N, 8·15%).

The 3 : 5-*dinitrobenzoate*, prepared and recrystallised in methanolic solution, formed orange-red crystals, m. p. 173—174° (Found: C, 56·3; H, 4·95; N, 10·7. $C_{19}H_{21}O_2N_2Cl,C_7H_4O_6N_2$ requires C, 56·1; H, 4·5; N, 10·1%). Persistently high nitrogen values were obtained on analysis.

7-*Chloro*-2-(2-*di*-n-*butylaminoethylamino*)*xanthone*.—2-Di-*n*-butylaminoethyl chloride hydrochloride (4·7 g.) was shaken with cold aqueous potassium carbonate and xylene (93 c.c.). The xylene layer was separated, dried, and heated under reflux with 2-amino-7-chloroxanthone (2 g.) during 40 hours. The *base* (0·6 g.), isolated as in the case of the ethyl analogue, was recrystallised from dilute ethanol, giving glistening golden-yellow plates, m. p. 105—106° (Found: C, 69·3; H, 7·4; N, 7·3. $C_{29}H_{29}O_2N_2Cl$ requires C, 68·9; H, 7·3; N, 7·0%).

2-(2-*Diethylaminoethylamino*)-6 : 8-*dimethylxanthone*.—A mixture of 2-amino-6 : 8-dimethylxanthone (5·8 g.) and 2-diethylaminoethyl chloride hydrochloride (5 g.) was heated for 1 hour at 150—155°. The *base*, isolated as in the foregoing experiments, crystallised from petroleum (b. p. 40—60°) and recrystallised from dilute ethanol (3 : 2 v/v; 60 c.c.) in glistening yellow needles (3·2 g.), m. p. 85—87° (Found: C, 74·6; H, 7·5; N, 8·5. $C_{21}H_{26}O_2N_2$ requires C, 74·5; H, 7·8; N, 8·3%).

The 3 : 5-*dinitrobenzoate*, prepared in methanolic solution, separated in red needles which were recrystallised from methanol giving yellow plates, m. p. 202—203° (Found: C, 61·05; H, 5·8; N, 10·3. $C_{21}H_{26}O_2N_2,C_7H_4O_6N_2$ requires C, 61·1; H, 5·5; N, 10·2%).

The *dihydrochloride*, prepared by adding cold saturated ethanolic hydrogen chloride (30 c.c.) to a solution of the base (3·0 g.) in warm ethanol (100 c.c.), crystallised in small faintly yellow needles (3·0 g.), m. p. 225° (decomp.), sintering at 215° (Found: N, 6·5. $C_{21}H_{26}O_2N_2,2HCl$ requires N, 6·8%).

The *chlorozincate* separated from the hot dilute zinc chloride reagent as a white microcrystalline powder, m. p. 240—242° (decomp.) (Found: C, 45·15; H, 5·25; N, 5·4. $C_{21}H_{26}O_2N_2,H_2ZnCl_4,\frac{1}{2}H_2O$ requires C, 45·3; H, 5·25; N, 5·1%). The salt gave a yellow solution in water.

3-(2-*Diethylaminoethylamino*)*xanthone* (IV; R = Et).—3-Aminoxanthone (1 g.) and 2-diethylaminoethyl chloride hydrochloride (0·9 g.) were heated together at 155—160° for 1 hour. The *base*, crystallised from light petroleum (b. p. 40—60°), had m. p. 87—89° (0·25 g.) (Found: C, 73·9; H, 7·2; N, 9·4. $C_{19}H_{22}O_2N_2$ requires C, 73·5; H, 7·2; N, 9·1%).

The 3 : 5-*dinitrobenzoate* crystallised from methanol in bright-yellow prisms, m. p. 172—174° (Found: C, 59·4; H, 5·3; N, 10·3. $C_{19}H_{22}O_2N_2,C_7H_4O_6N_2$ requires C, 59·8; H, 5·0; N, 10·7%).

The *chlorozincate* (0·12 g.), m. p. 213°, slowly separated on mixing of a hot concentrated ethanolic solution of the base (0·145 g.) with 2% zinc chloride in concentrated hydrochloric acid. The salt crystallised in orange needles, m. p. 215° (decomp.) (Found: C, 43·6; H, 4·7; N, 5·4. $C_{19}H_{22}O_2N_2,H_2ZnCl_4$ requires C, 43·9; H, 4·7; N, 5·4%). An aqueous solution of the salt was colourless.

2-*Iodoxanthone*.—This compound has been prepared by Brewster and Strain (*J. Amer. Chem. Soc.*, 1934, **56**, 118) by the cyclisation of *o*-*p*′-iodophenoxybenzoic acid. Alternatively, a solution of 2-aminoxanthone (1 g.) in hot acetic acid (12 c.c.) was cooled with vigorous shaking, and slowly added to a solution of sodium nitrite (0·4 g.) in concentrated sulphuric acid (3 c.c.) at 15—20°. This mixture after 2 hours was in turn added with stirring to a solution of potassium iodide (5 g.) and hydrated sodium acetate (17 g.) in cold water (20 c.c.). The brown suspension was diluted with water, boiled, and filtered hot. The insoluble 2-iodoxanthone was sublimed at 200°/0·1 mm. and then recrystallised from ethanol, giving needles (0·8 g.), m. p. 160—161° (Found: C, 48·8; H, 2·6. Calc. for $C_{13}H_7O_2I$: C, 48·5; H, 2·2%).

Di-(2-*diethylaminoethyl*)*amine*.—2-Diethylaminoethyl chloride hydrochloride (50 g.) was shaken with xylene (120 c.c.) and aqueous potassium carbonate. A mixture of this xylene solution and 2-diethylaminoethylamine (58 g.) was heated at 100° for 32 hours, and after basification furnished the *triamine* as a hygroscopic liquid (33 g.), b. p. 155—157°/50 mm. (Found: N, 19·5. $C_{12}H_{29}N_3$ requires N, 19·5%). The *tripicrate* separated from methanol in yellow plates, m. p. 163—165° (Found: C, 40·2; H, 4·0; N, 18·6. $C_{12}H_{29}N_3,3C_6H_3O_7N_3$ requires C, 39·9; H, 4·25; N, 18·6%).

2-*Nitrothioxanthone* (XI).—*The sodium derivative of methyl* o-*mercaptobenzoate*. A solution of methyl *o*-mercaptobenzoate (17·6 g.), prepared by Gattermann's method (*Ber.*, 1899, **32**, 1150), in methanol (16 c.c.) was mixed with a solution of sodium (2·4 g.) in methanol (40 c.c.) at 0°. The mixture was evaporated to dryness at 30° in a vacuum, and the residue washed with ether and dried *in vacuo*, yielding a pale-yellow solid (20 g.).

o-*Carbomethoxyphenyl* p-*nitrophenyl sulphide* (X). The foregoing sodium derivative (7·5 g.) and *p*-chloronitrobenzene (15 g.) were heated to 160° for 30 minutes; the mass melted and effervesced. When the reaction had subsided, the product was cooled and acidified with hydrochloric acid, and unchanged *p*-chloronitrobenzene removed by steam-distillation. The residual suspension crystallised on cooling, giving the crude methyl ester which was recrystallised from methanol, giving pale-yellow crystals (7·3 g.), m. p. 131—132° (Found: C, 58·3; H, 3·8; N, 5·1. Calc. for $C_{14}H_{11}O_4NS$: C, 58·1; H, 3·8; N, 4·85%). Mayer (*loc. cit.*) records m. p. 131·5°.

o-*Carboxyphenyl* p-*nitrophenyl sulphide*. The ester (8·3 g.) was hydrolysed by boiling it under reflux with N-potassium hydroxide (160 c.c.) for 6 hours. The carboxylic acid crystallised from ethanol as pale-yellow crystals (6·6 g.), m. p. 227—228° (Found: C, 56·8; H, 3·4; N, 5·45. Calc. for $C_{13}H_9O_4NS$: C, 56·7; H, 3·30; N, 5·1%). Mayer records m. p. 229—231°, sintering at 210°.

The thioxanthone. This acid (2 g.) was converted into the acid chloride and cyclised by treatment with aluminium chloride in the usual way. This gave 2-nitrothioxanthone (1·55 g.), m. p. 221—223°

which was recrystallised from glacial acetic acid, forming pale-yellow silky needles, m. p. 224—225° (Found: C, 60·4; H, 2·7; N, 5·8. Calc. for $C_{13}H_7O_3NS$: C, 60·7; H, 2·7; N, 5·5%). Mayer (*loc. cit.*) records m. p. 219—221°.

7-*Methyl*-2-*nitrothioxanthone*.—5-*Methylanthranilic acid*. This acid, prepared from 5-methylisatin (20 g.) by Mayer, Schäfer, and Rosenbach's method (*Arch. Pharm.*, 1929, **267**, 579), was obtained as a pale-brown solid (17 g.), m. p. 168—173°. Mayer *et al.* record m. p. 175°.

4-*Mercapto*-m-*toluic acid*. The anthranilic acid (26 g.) was diazotised and then treated with sodium polysulphide, as described for anthranilic acid itself (*Org. Synth.*, Coll. Vol. II, p. 580), giving 4-mercapto-*m*-toluic acid (20·5 g.), m. p. 155—157°. Krollpfeiffer (*Ber.*, 1925, **58**, 1668) records m. p. 155—157°.

Methyl 4-*mercapto*-m-*toluate*. A solution of the acid (20 g.) in methanol (100 c.c.) was heated under reflux for 3 hours in a stream of dry hydrogen chloride. The product was cooled and poured on ice, whereupon the *ester* (18 g.), m. p. 58—60°, crystallised. It was collected, dried, and distilled, giving a liquid, b. p. 85—87°/0·5 mm., which solidified and was then recrystallised from methanol forming white crystals, m. p. 61—62° (Found: C, 59·3; H, 5·6. $C_9H_{10}O_2S$ requires C, 59·3; H, 5·5%).

3-*Carbomethoxy*-p-*tolyl* p-*nitrophenyl sulphide*. The sodio-derivative (6·7 g.) of the methyl toluate, prepared in the usual way, was mixed with *p*-chloronitrobenzene (14 g.) and heated at 165—170° for 2 hours. The product was cooled, acidified with hydrochloric acid, and steam-distilled to remove the excess of *p*-chloronitrobenzene. The residual suspension crystallised on cooling, giving the required *ester* (8·3 g.) which was recrystallised from methanol, forming yellow crystals (6·1 g.), m. p. 113—114° (Found: C, 59·5; H, 4·4; N, 4·7. $C_{15}H_{13}O_4NS$ requires C, 59·4; H, 4·3; N, 4·6%).

3-*Carboxy*-p-*tolyl* p-*nitrophenyl sulphide*. The ester (4·6 g.) was hydrolysed by heating it under reflux with N-potassium hydroxide (100 c.c.) for 3 hours. The *acid* was sublimed at 165—170°/0·1 mm., giving a yellow solid (2·5 g.), m. p. 178—180° which crystallised from benzene in pale-yellow crystals, m. p. 178—180° (Found: C, 58·5; H, 4·1; N, 4·9. $C_{14}H_{11}O_4NS$ requires C, 58·1; H, 3·8; N, 4·8%).

The thioxanthone. This acid (4 g.) was converted into the chloride and cyclised with aluminium chloride in nitrobenzene. The product was sublimed at 230°/0·1 mm., giving the thioxanthone as a yellow solid (1·85 g.), m. p. 257—260° (Found: C, 61·9; H, 3·4; N, 5·0. Calc. for $C_{14}H_9O_3NS$: C, 62·0; H, 3·3; N, 5·2%). Campbell, Dick, Ferguson, and Loudon (*J.*, 1941, 750) give m. p. 262°.

6 : 8-*Dimethyl*-2-*nitrothioxanthone*.—5-*Nitro*-m-*xylene*. Concentrated sulphuric acid (125 c.c.) was added gradually to a hot solution of 5-nitro-*m*-4-xylidine (195 g.) in ethanol (1560 c.c.). The mixture was heated on the water-bath until it began to reflux; it was then removed and powdered sodium nitrite (244 g.) added in small portions during 1 hour, with occasional shaking. The product was heated under reflux on the water-bath for 45 minutes, diluted with water, and steam-distilled until no more yellow solid passed over. The crude nitroxylene (90 g.) crystallised from petroleum (b. p. 40—60°) as a yellow solid (64 g.), m. p. 66—68°, which formed pale-yellow crystals, m. p. 71—72°, from methanol (Found: C, 63·8; H, 5·95; N, 9·6. Calc. for $C_8H_9O_2N$: C, 63·6; H, 6·0; N, 9·3%). Jacobson (*Annalen*, 1922, **427**, 207) gives m. p. 71°.

m-5-*Xylidine*. The nitroxylene (59 g.) was dissolved in ethanol (480 c.c.), stannous chloride (320 g.) in concentrated hydrochloric acid (355 c.c.) was added, and the solution set aside for 1 hour and finally warmed on the water-bath for 3 hours. The product was diluted with water and basified with an excess of 5N-sodium hydroxide. The amine, isolated by extraction with ether, distilled as a colourless liquid (38 g.), b. p. 114—117°/20 mm. The acetyl derivative crystallised from dilute ethanol in plates, m. p. 139—141° (Found: C, 73·7; H, 8·1; N, 8·7. Calc. for $C_{10}H_{13}ON$: C, 73·6; H, 8·0; N, 8·6%).

Oximinoacet-m-5-*xylidide*. This compound was prepared from the amine (60·5 g.) by using the method described for oximinoacetanilide (*Org. Synth.*, Coll. Vol. I, p. 327); the crude air-dried product weighed 70 g.

4 : 6-*Dimethylisatin*. The oximino-compound (50 g.) was gradually added to a well-stirred mixture of concentrated sulphuric acid (200 c.c.) and water (20 c.c.) at 50°. The temperature was allowed to rise to 60—70° during the addition, and when this was complete the mixture was warmed to 80° for 10 minutes, cooled, and poured on ice. The *isatin* was precipitated as an orange solid which was collected, thoroughly washed with water, and dried in the air; it (29 g.) had m. p. 200—215°. A portion was extracted with benzene (Soxhlet), and the extracts deposited a solid which crystallised from glacial acetic in glistening orange crystals, m. p. 241—243° (Found: C, 68·6; H, 5·0; N, 8·35. $C_{10}H_9O_2N$ requires C, 68·6; H, 5·2; N, 8·0%).

4 : 6-*Dimethylanthranilic acid*. The crude isatin (29 g.) was suspended in hot water (100 c.c.) and N-sodium hydroxide (100 c.c.) added with stirring. The solution was filtered from tarry matter, hot N-sodium hydroxide (150 c.c.) added to the filtrate, and hydrogen peroxide (10%; 120 c.c.) dropped in at 100° during 30 minutes with stirring. The solution was cooled, filtered, and made slightly acid (Congo-red) by the addition of dilute hydrochloric acid, whereupon the anthranilic acid was slowly deposited. The crude product (17·5 g.) was used directly without further purification.

2-*Mercapto*-4 : 6-*dimethylbenzoic acid*. The anthranilic acid was converted into the corresponding mercapto-acid by essentially the same procedure as that employed in the preparation of 4-mercapto-*m*-toluic acid. The *acid*, isolated as a white solid (9·1 g.), m. p. 130—135°, recrystallised from petroleum (b. p. 60—80°) as pale-yellow rosettes, m. p. 138—140° (Found: C, 58·8; H, 5·85. $C_9H_{10}O_2S$ requires C, 59·4; H, 5·5%).

Methyl 2-*mercapto*-4 : 6-*dimethylbenzoate*. The acid (8 g.) was dissolved in methanol (100 c.c.) and heated under reflux in a stream of dry hydrogen chloride for 10 hours. The ester (4 g.) was obtained as a liquid of unpleasant odour, b. p. 160—165°/25 mm. Further amounts of ester could be obtained by re-esterification of the residue after distillation.

4-*Carbomethoxy*-m-5-*xylyl* p-*nitrophenyl sulphide*. The sodium derivative (1·4 g.) of the above ester was mixed with *p*-chloronitrobenzene (3·8 g.) and heated to 155° during 10 minutes, and the temperature maintained at 155° for a further 30 minutes. The product was cooled and acidified, and the excess of *p*-chloronitrobenzene removed by steam-distillation. The residual oily suspension slowly crystallised to give the crude *ester* which formed pale-yellow plates (1·5 g.), m. p. 79—80°, from methanol (Found: C, 60·8; H, 4·9; N, 4·4. $C_{16}H_{15}O_4NS$ requires C, 60·6; H, 4·8; N, 4·4%).

The thioxanthone. The ester (200 mg.) was dissolved in concentrated sulphuric acid (2 c.c.) and heated at 100° for 3 hours. The product was cooled and poured on ice, and the pale-yellow *thioxanthone* collected, thoroughly washed with water and sodium hydroxide, dried at 100° (150 mg.), and recrystallised first from glacial acetic acid and then from ethanol, giving minute, pale-yellow needles, m. p. 225—226° (Found: C, 63·5; H, 4·3; N, 5·1. $C_{15}H_{11}O_3NS$ requires C, 63·1; H, 3·9; N, 4·9%).

7-*Chloro*-2-*nitrothioxanthone* (XII). *Method I.*—5-*Chloro*-2-*mercaptobenzoic acid*. Methyl 5-chloroanthranilate (21 g.) (Freundler, *Bull. Soc. chim.*, 1911, [iv], **9**, 606) was hydrolysed by boiling it with N-potassium hydroxide (420 c.c.) for 1 hour. The resulting 5-chloroanthranilic acid (20 g.), m. p. 208—210°, was diazotised and converted into the mercapto-acid as for the *m*-toluic acid. 5-Chloro-2-mercaptobenzoic acid was obtained as a solid (16 g.), m. p. 188—190°, which crystallised from benzene in pale-yellow needles, m. p. 190—192° (Found: C, 44·8; H, 2·8. Calc. for $C_7H_5O_2ClS$: C, 44·6; H, 2·7%). Hart and McClelland (*J.*, 1938, 2114) give m. p. 193°.

Methyl 5-*chloro*-2-*mercaptobenzoate*. A solution of this acid (15 g.) in methanol (200 c.c.) was heated under reflux for 3 hours in a stream of dry hydrogen chloride. The mixture was cooled, and poured on ice, and the *ester* collected, dried (15 g.) and distilled, giving a liquid (b. p. 110—112°/0·5 mm.) which rapidly solidified. The solid (12 g.) crystallised from petroleum (b. p. 40—60°) in clusters of white needles, m. p. 45—47° (Found: C, 47·6; H, 3·65. $C_8H_7O_2ClS$ requires C, 47·4; H, 3·5%). The ester was readily soluble in cold sodium hydrogen carbonate solution.

2-*Carbomethoxy*-4-*chlorophenyl* p-*nitrophenyl sulphide*. The sodium derivative (7 g.) of the above ester was mixed with *p*-chloronitrobenzene (14 g.) and heated to 155° during 10 minutes, and the temperature maintained at 155° for a further 30 minutes. The product was cooled and acidified with hydrochloric acid, and excess of *p*-chloronitrobenzene removed by steam-distillation. The residual oily suspension crystallised on cooling, and the crude *ester* was recrystallised from methanol, giving pale yellow prisms (6·2 g.), m. p. 114—115° (Found: C, 52·2; H, 3·0; N, 4·5. $C_{14}H_{10}O_4NClS$ requires C, 51·9; H, 3·1; N, 4·3%).

2-*Carboxy*-4-*chlorophenyl* p-*nitrophenyl sulphide*. The ester (6·2 g.) and N-potassium hydroxide (120 c.c.) were heated under reflux for 3 hours. The *acid* crystallised from toluene in yellow crystals (5·3 g.), m. p. 207—208° (Found: C, 50·7; H, 2·75; N, 4·4. $C_{13}H_8O_4NClS$ requires C, 50·4; H, 2·6; N, 4·5%).

The thioxanthone (XII). The acid (5 g.) was mixed with benzene (50 c.c.) and warmed on the water-bath with thionyl chloride (5 c.c.) for 3 hours. The benzene was removed, and the residue dissolved in warm nitrobenzene (50 c.c.) and cooled rapidly with vigorous shaking, whereupon the acid chloride separated as a fine precipitate. A cold solution of aluminium chloride (5 g.) in nitrobenzene (50 c.c.) was dropped into the suspension at 0°, the mixture set aside at 0° overnight, and decomposed by the addition of ice, and the nitrobenzene removed by steam-distillation. The residual solution was cooled and the tarry amorphous deposit collected, dried, and boiled with glacial acetic acid (60 c.c.) for 1 hour. The solution was cooled and the *thioxanthone* collected, washed with glacial acetic acid, water, and dilute sodium hydroxide solution, and then dried, yielding a brown solid (1·39 g.), m. p. 267—270°, which was sublimed (230°/0·5 mm.) and recrystallised from glacial acetic acid (500 c.c.), forming small pale-yellow plates (1 g.), m. p. 271—272° (Found: C, 53·5; H, 1·7; H, 4·9. $C_{13}H_6O_3NClS$ requires C, 53·5; H, 2·1; N, 4·8).

7-*Chloro*-2-*nitrothioxanthone* (XII). *Method 2.*—5-*Nitroanthranilic acid*. Acetylanthranilic acid (100 g.) was gradually stirred into concentrated sulphuric acid (270 c.c.) at 0—5°. A mixture of nitric acid (*d* 1·5; 30 c.c.) and concentrated sulphuric acid (50 c.c.) was then slowly dropped in at <5°, the product maintained at 0—5° for a further 4 hours and then poured on ice, and the crude nitro-acid (120 g.; m. p. 155—160°) collected. The acetyl group was removed by stirring the product into concentrated hydrochloric acid (600 c.c.) at 100° during ½ hour. The mixture was poured into water and the nitroanthranilic acid (63 g.), m. p. 263° (decomp.), recrystallised from methanol and finally from water, giving small orange-yellow needles, m. p. 270—273° (decomp.) (Found: N, 15·6. Calc. for $C_7H_6O_4N_2$: N, 15·4%). Rupe (*loc. cit.*) records m. p. 263°.

2-*Carbomethoxy*-4-*nitrophenyl* p-*chlorophenyl sulphide*. 5-Nitroanthranilic acid (42 g.) was ground with concentrated hydrochloric acid (284 c.c.) at 0° and diazotised by the gradual addition of an aqueous solution of sodium nitrite (10%; 168 c.c.) during 2 hours. The diazo-solution was filtered and slowly added to a well-stirred solution of *p*-chlorothiophenol (33·6 g.) in aqueous potassium hydroxide (potassium hydroxide, 212 g., and water, 656 c.c.) at 55—60°. The temperature of the mixture was raised to 100° during 30 minutes, then cooled, and acidified, and the solid collected, dried, and extracted with benzene (Soxhlet). The extracts deposited the crude acid, m. p. 228—230° (25 g.), which was converted into the *methyl* ester (24 g.), which crystallised from methanol in pale yellow prisms, m. p. 145—146° (Found: C, 52·0; H, 2·9; N, 4·5. $C_{14}H_{10}O_4NClS$ requires C, 51·9; H, 3·1; N, 4·3%).

2-*Carboxy*-4-*nitrophenyl* p-*chlorophenyl sulphide* (XIII). The ester (4·3 g.) and N-potassium hydroxide were boiled under reflux for 1 hour. The *acid* (3·8 g.) was recrystallised from benzene and finally from methanol, giving pale yellow crystals, m. p. 234—235° (Found: C, 50·4; H, 2·7; N, 4·5. $C_{13}H_8O_4NClS$ requires C, 50·4; H, 2·6; N, 4·5%).

The thioxanthone (XII). This was prepared by conversion of the acid (2·9 g.) into the acid chloride which was subsequently treated with aluminium chloride in the usual way. The solid product (2·6 g.)

crystallised from glacial acetic acid (1000 c.c.) in small pale yellow plates, m. p. 269—271°, identical with 7-chloro-2-nitrothioxanthone prepared by method I (Found: C, 53·85; H, 2·2; N, 4·9%).

3-*Nitrothioxanthone*—2-*Carbomethoxy*-5-*nitrophenyl phenyl sulphide*. 4-Nitroanthranilic acid (5·3 g.) (Wheeler and Johns, *Amer. Chem. J.*, 1910, **44**, 443) was ground in a mortar with cold concentrated hydrochloric acid (24 c.c.), cooled in ice for 10 minutes, and diazotised by the gradual addition of sodium nitrite solution (10%; 21—24 c.c.) at 0—5°. The diazotised product was diluted with ice–water (40 c.c.), filtered, and dropped into a well-stirred solution of thiophenol (3·3 g.) and potassium hydroxide (26·4 g.) in water (80 c.c.) during 1 hour at 55—60°. The temperature of the mixture was then raised to 85°, and stirring was continued for a further hour. The product was acidified with hydrochloric acid, and the precipitate dried (7·5 g.) and extracted with benzene (100 c.c.) (Soxhlet). The benzene extracts deposited the crude carboxylic acid (4 g.), m. p. 200—208°, which was dissolved in methanol (100 c.c.) and esterified by boiling it for 3 hours in a stream of dry hydrogen chloride. The *methyl* ester (3·9 g.) recrystallised from methanol as bright-yellow plates, m. p. 102—103° (Found: C, 58·4; H, 3·8; N, 5·05. $C_{14}H_{11}O_4NS$ requires C, 58·1; H, 3·8; N, 4·85%).

2-*Carboxy*-5-*nitrophenyl phenyl sulphide*. The ester (2·2 g.) was hydrolysed by boiling it with N-potassium hydroxide (40 c.c.) for 3 hours. The acid (2 g.) was recrystallised from benzene, forming bright-yellow needles, m. p. 213—215° (Found: C, 56·7; H, 3·1; N, 5·2. Calc. for $C_{13}H_9O_4NS$: C, 56·7; H, 3·3; N, 5·1%). Mayer (*loc. cit.*) records m. p. 210—211°.

The thioxanthone. The above acid (1·4 g.) was converted into the acid chloride by treatment with thionyl chloride (1·4 c.c.) in benzene (14 c.c.). The product was treated with aluminium chloride in the standard way, to give 3-nitrothioxanthone (1·2 g.), m. p. 252°, which crystallised from glacial acetic acid in golden-yellow plates, m. p. 252° (Found: C, 60·7; H, 2·9; N, 5·8. Calc. for $C_{13}H_7O_3NS$: C, 60·7; H, 2·7; N, 5·5%).

7-*Chloro*-3-*nitrothioxanthone*.—2-*Carbomethoxy*-5-*nitrophenyl* p-*chlorophenyl sulphide*. 4-Nitroanthranilic acid (5·3 g.) was diazotised and the diazo-solution dropped into *p*-chlorothiophenol (4·2 g.) in potassium hydroxide solution (potassium hydroxide, 26·4 g., in water, 80 c.c.) as in the foregoing experiments. The crude acid (3·6 g.), purified by benzene extraction, had m. p. 213—216° and was converted into the *methyl* ester (3 g.) which crystallised from methanol in slender pale-yellow needles, m. p. 139—140° (Found: C, 52·2; H, 3·0; N, 4·6. $C_{14}H_{10}O_4NClS$ requires C, 51·9; H, 3·1; N, 4·3%).

2-*Carboxy*-5-*nitrophenyl* p-*chlorophenyl sulphide*. The ester (2·5 g.) was hydrolysed by boiling it under reflux with N-potassium hydroxide (45 c.c.) for 3 hours. The *acid* crystallised from benzene in small pale-yellow needles (1·3 g.), m. p. 217—219° (Found: C, 50·3; H, 2·4; N, 4·8. $C_{13}H_8O_4NClS$ requires C, 50·4; H, 2·6; N, 4·5%).

The thioxanthone. The acid (1·2 g.) was converted into the acid chloride and cyclised in the standard way, to give the required *thioxanthone*, which sublimed at 280°/0·1 mm. (0·9 g.; m. p. 322—323°) and was recrystallised from a large volume of glacial acetic acid forming small yellow needles (Found: C, 53·8; H, 1·7; N, 4·9. $C_{13}H_6O_3NClS$ requires C, 53·5; H, 2·1; N, 4·8%).

7-*Methyl*-3-*nitrothioxanthone*.—2-*Carbomethoxy*-5-*nitrophenyl* p-*tolyl sulphide*. 4-Nitroanthranilic acid (5·3 g.) was diazotised in hydrochloric acid, and the diazo-solution dropped into thio-*p*-cresol (3·7 g.) in potassium hydroxide solution, essentially the same method as that described for the preparation of 2-carboxy-5-nitrophenyl phenyl sulphide being used. The crude *acid* (3·3 g.; m. p. *ca.* 230°), isolated by benzene extraction, was recrystallised from toluene, and the product (2·5 g.) dissolved in methanol (100 c.c.) and converted into the *methyl* ester which crystallised from methanol in yellow prisms (2·0 g.), m. p. 112—114° (Found: C, 59·3; H, 4·5; N, 4·7. $C_{15}H_{11}O_4NS$ requires C, 59·4; H, 4·3; N, 4·6%).

2-*Carboxy*-5-*nitrophenyl* p-*tolyl sulphide*. The ester (2·2 g.) was hydrolysed by boiling it with N-potassium hydroxide (40 c.c.) for 2 hours. The *acid* (2·1 g.), m. p. 233—235°, recrystallised from toluene as bright-yellow needles (1·5 g.), m. p. 235—237° (Found: C, 58·0; H, 3·5; N, 4·6. $C_{14}H_{11}O_4NS$ requires C, 58·1; H, 3·8; N, 4·8%).

The thioxanthone. The foregoing acid (2·0 g.) was converted into the acid chloride and cyclised to give the thioxanthone (1·8 g.) which crystallised from glacial acetic acid in glistening orange-yellow needles, m. p. 274—275° (Found: C, 62·4; H, 3·6; N, 5·15. Calc. for $C_{14}H_9O_3NS$: C, 62·0; H, 3·3; N, 5·2%). Campbell *et al.* (*loc. cit.*) give m. p. 276°.

2-*Aminothioxanthone*.—2-Nitrothioxanthone (0·4 g.) was suspended in acetic acid (6 c.c.), a solution of stannous chloride (1·64 g.) in concentrated hydrochloric acid (2·5 c.c.) added, and the mixture warmed for 2 hours on the water-bath. The solid was collected, reduced again under the same conditions, and digested with 2·5N-sodium hydroxide; the amine recrystallised from ethanol, giving orange needles (0·25 g.), m. p. 227—228° (Found: C, 68·9; H, 3·95; N, 6·5. Calc. for $C_{13}H_9ONS$: C, 68·7; H, 4·0; N, 6·2%). Mayer (*loc. cit.*) records m. p. 221—222°.

2-*Amino*-7-*chlorothioxanthone*.—2-Chloro-7-nitrothioxanthone was similarly reduced and the *amine* recrystallised from ethanol, giving glistening orange needles, m. p. 228—230° (Found: C, 59·2; H, 2·8; N, 5·6. $C_{13}H_8ONClS$ requires C, 59·7; H, 3·1; N, 5·4%).

2-*Amino*-7-*methylthioxanthone*.—7-Methyl-2-nitrothioxanthone was reduced as above and the *amine* recrystallised from ethanol, giving glistening orange crystals, m. p. 194—195° (Found: C, 69·9; H, 4·9; N, 5·8. $C_{14}H_{11}ONS$ requires C, 69·7; H, 4·6; N, 5·8%).

3-*Aminothioxanthone*. This was similarly prepared by the reduction of 3-nitrothioxanthone; it crystallised from ethanol in pale-yellow needles, m. p. 252—254° (Found: C, 68·8; H, 4·1; N, 6·0. Calc. for $C_{13}H_9ONS$: C, 68·7; H, 4·0; N, 6·2%). Mayer (*loc. cit.*) gives m. p. 246°.

3-*Amino*-7-*chlorothioxanthone*. This *compound*, similarly prepared, also crystallised from ethanol in pale-yellow needles, m. p. 278—279° (Found: C, 59·7; H, 3·4; N, 5·6. $C_{13}H_8ONClS$ requires C, 59·7; H, 3·1; N, 5·4%).

3-*Amino*-7-*methylthioxanthone*. This *compound* was similarly prepared; it separated from ethanol in pale-yellow plates, m. p. 234—236° (Found: C, 69·9; H, 4·55; N, 5·6. $C_{14}H_{11}ONS$ requires C, 69·7; H, 4·6; N, 5·8%).

2-(2-*Diethylaminoethylamino*)*thioxanthone* (XIV; R = Et).—2-Aminothioxanthone (1·0 g.) and 2-diethylaminoethyl chloride hydrochloride (0·85 g.) were heated at 170° for 1 hour. The *base* (0·52 g.), isolated as in the xanthone series, crystallised from petroleum (b. p. 40—60°) in glistening orange plates, m. p. 52—53° (Found: C, 69·8; H, 7·1; N, 8·4. $C_{19}H_{22}ON_2S$ requires C, 69·9; H, 6·8; N, 8·6%). The *dinitrobenzoate* crystallised from methanol in ruby-red crystals, m. p. 183—184° (Found: C, 58·0; H, 4·8; N, 10·5. $C_{19}H_{22}ON_2S,C_7H_4O_6N_2$ requires C, 58·0; H, 4·9; N, 10·4%). The *picrate* crystallised from methanol in clusters of golden-yellow needles, m. p. 178—180° (Found: C, 54·0; H, 4·5; N, 12·6. $C_{19}H_{22}ON_2S,C_6H_3O_7N_3$ requires C, 54·0; H, 4·5; N, 12·6%). The *dihydrochloride*, prepared by adding saturated ethanolic hydrogen chloride (30 c.c.) to a warm solution of the base (3·0 g.) in ethanol (150 c.c.), crystallised in small pale yellow plates (3·75 g.), m. p. 220° (decomp.) (Found: N, 7·0. $C_{19}H_{22}ON_2S,2HCl$ requires N, 6·85%).

The *chlorozincate*, prepared in a similar way to the analogous salt in the xanthone series, crystallised from the hot dilute zinc chloride reagent in greenish-white needles, m. p. 255° (decomp.) (Found: C, 42·6; H, 4·5; N, 5·0. $C_{19}H_{22}ON_2S,H_2ZnCl_4$ requires C, 42·6; H, 4·5; N, 5·2%). The salt gave an intense yellow solution in water.

7-*Chloro*-2-(2-*diethylaminoethylamino*)*thioxanthone*.—7-Chloro-2-aminothioxanthone (2·25 g.) and 2-diethylaminoethyl chloride hydrochloride (1·7 g.) were heated at 160—165° for 1 hour. The *base* (1·0 g.) crystallised from petroleum (b. p. 40—60°) in lustrous orange-red plates, m. p. 128—129° (Found: C, 63·6; H, 5·8; N, 7·7. $C_{19}H_{21}ON_2ClS$ requires C, 63·2; H, 5·85; N, 7·8%). The *dihydrochloride* prepared by adding saturated ethanolic hydrogen chloride (9 c.c.) to a solution of the base (0·9 g.) in ethanol (70 c.c.), crystallised as minute pale yellow needles (1·05 g.), m. p. 255° (decomp.) (Found: N, 6·7. $C_{19}H_{21}ON_2ClS,2HCl$ requires N, 6·5%). The *dinitrobenzoate* crystallised from methanol in red needles, m. p. 183—184° (Found: C, 54·45; H, 4·5; N, 9·6. $C_{19}H_{21}ON_2ClS,C_7H_4O_6N_2$ requires C, 54·5; H, 4·4; N, 9·8%).

The *chlorozincate* crystallised from the dilute zinc chloride reagent in minute white needles, m. p. 270° (decomp.) (Found: C, 40·1; H, 4·2; N, 4·8. $C_{19}H_{21}ON_2ClS,H_2ZnCl_4$ requires C, 40·0; H, 4·1; N, 4·9%). The salt gave a bright yellow solution in water.

7-*Chloro*-2-(2-*di*-n-*butylaminoethylamino*)*thioxanthone*.—2-Amino-7-chlorothioxanthone (1·5 g.) was alkylated with 2-di-*n*-butylaminoethyl chloride in a similar way to the corresponding condensation in the xanthone series. The *base* (0·9 g.) recrystallised from dilute ethanol in small orange-red needles, m. p. 104—105° (Found: C, 66·5; H, 6·9; N, 7·05. $C_{23}H_{29}ON_2ClS$ requires C, 66·2; H, 7·0; N, 6·7%).

2-(2-*Diethylaminoethylamino*)-7-*methylthioxanthone*.—2-Amino-7-methylthioxanthone (0·63 g.) and 2-diethylaminoethyl chloride hydrochloride (0·54 g.) were heated at 155° during 1 hour. The *base* (6·25 g.) crystallised from petroleum (b. p. 40—60°) in glistening orange plates, m. p. 73—75° (Found: C, 70·1; H, 6·8; N, 8·3. $C_{20}H_{24}ON_2S$ requires C, 70·5; H, 7·1; N, 8·2%). The *dinitrobenzoate* crystallised from methanol in small orange-red needles, m. p. 186—187° (Found: C, 58·85; H, 5·25; N, 10·0. $C_{20}H_{24}ON_2S,C_7H_4O_6N_2$ requires C, 58·7; H, 5·1; N, 10·1%). The *dihydrochloride* crystallised in small pale-yellow plates, m. p. 255° (decomp.) (Found: N, 6·7. $C_{20}H_{24}ON_2S,2HCl$ requires N, 6·8%).

The *chlorozincate* crystallised from the dilute zinc chloride reagent in pale yellow needles, m. p. 272° (decomp.) (Found: C, 44·0; H, 4·8; N, 5·1. $C_{20}H_{24}ON_2S,H_2ZnCl_4$ requires C, 43·7; H, 4·8; N, 5·1%). The salt gave an intense yellow solution in water.

3-(2-*Diethylaminoethylamino*)*thioxanthone* (XV; R = Et).—This *thioxanthone* was prepared precisely as the 2-substituent analogue; it crystallised from petroleum (b. p. 40—60°) in pale yellow plates, m. p. 91—92° (Found: C, 70·0; H, 7·1; N, 8·5. $C_{19}H_{22}ON_2S$ requires C, 69·9; H, 6·8; N, 8·6%). The *dinitrobenzoate* crystallised from methanol in yellow plates, m. p. 189—190° (Found: C, 58·0; H, 5·1; N, 10·4%). The *chlorozincate* separated when a hot concentrated ethanolic solution of the base was mixed with 2% zinc chloride in concentrated hydrochloric acid. The salt was recrystallised from the concentrated reagent, giving glistening vermilion plates, m. p. 240—245° (decomp.), sintering at 235° (Found: C, 42·7; H, 4·7; N, 5·1%).

7-*Chloro*-3-(2-*diethylaminoethylamino*)*thioxanthone*.—This *compound*, similarly prepared, crystallised from petroleum (b. p. 100—120°) as an orange solid which was recrystallised from ethanol, forming pale golden plates, m. p. 112—113° (Found: C, 63·4; H, 5·8; N, 7·6%). The *dinitrobenzoate* formed yellow crystals (from methanol), m. p. 197—198° (Found: C, 54·4; H, 4·5; N, 9·7%).

3-(2-*Diethylaminoethylamino*)-7-*methylthioxanthone*.—This *base* was similarly prepared; it crystallised from petroleum (b. p. 40—60°) in pale yellow crystals, m. p. 81—83° (Found: C, 70·6; H, 7·5; N, 8·2%). The *dinitrobenzoate* separated from methanol as yellow crystals, m. p. 186—188° (Found: C, 58·9; H, 5·5; N, 10·3%). The *chlorozincate* crystallised from the concentrated reagent in glistening orange plates, m. p. 232° (decomp.), sintering at 225° (Found: C, 43·7; H, 4·5; N, 5·21%). The salt gave a colourless solution in water. The *chlorocadmiate*, prepared by mixing a concentrated ethanolic solution of the base with 2% cadmium chloride in concentrated hydrochloric acid, was recrystallised from the reagent, giving orange crystals, m. p. 210° (decomp.) (Found: C, 40·0; H, 4·6; N, 4·8. $C_{20}H_{24}ON_2S,H_2CdCl_4$ requires C, 40·3; H, 4·4; N, 4·7%).

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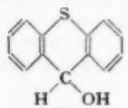
163. *Xanthones and Thioxanthones. Part II. Derivatives of Thioxanthhydrol, 9-Xanthylamine, and 9-Thioxanthylamine.*

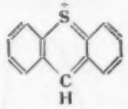
By Frederick G. Mann and J. Hedley Turnbull.

2- and 3-(2-Diethylaminoethylamino)thioxanthones and also their 7-chloro- and 7-methyl derivatives have been reduced to the corresponding hydrols, and the latter in turn converted into their perchlorate hydrogen perchlorate salts, (V) and (VI). The two isomeric series of salts are entirely different in properties, the 2-substituted compounds forming blue-black crystals which hydrolyse in water, whilst the 3-substituted compounds form stable crimson crystals. In each series the corresponding chlorozincates are similar in appearance and properties to the perchlorates. The reason for this marked difference between the two series is discussed.

9-Xanthylamine and di-9-xanthylamine, and their thio-analogues, have been synthesised. They undergo very ready hydrolysis by acids, even at room temperature, with loss of ammonia, and synthetic work on their derivatives was therefore discontinued.

It is known that thioxanthone, like xanthone itself, can be reduced to the corresponding hydrol (I). The thioxanthhydrol thus produced acts as a weak base, and with acids gives rise to salts in which the cation must have a resonance structure to which the sulphonium form (II) and carbonium forms, such as (III) and (IV), contribute. Of these, the major contribution is


(I.)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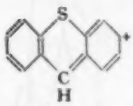
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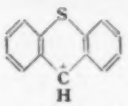
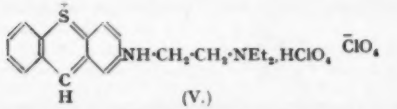

(IV.)

probably made by the sulphonium form (II), for the " aromatic " structure of the central ring would give enhanced stability to this form. Nevertheless, salts of both xanthhydrol and thioxanthhydrol undergo ready dissociation in water (Werner, *Ber.*, 1901, **34**, 3302; Hilditch and Smiles, *J.*, 1911, **99**, 157; *cf.* also Gomberg and Cone, *Annalen*, 1910, **376**, 188; Kehrmann, *Annalen*, 1910, **372**, 307).

We have studied in some detail the reduction products of the 2- and 3-(2-diethylaminoethylamino)thioxanthones described in the previous paper. The former on reduction gave the corresponding thioxanthhydrol as an unstable gum which, however, on treatment with perchloric acid gave the crystalline perchlorate hydrogen perchlorate of composition (V). In this salt the hydrogen perchlorate undoubtedly neutralises the terminal tertiary group; the latter is normally more strongly basic than the secondary amine group, which moreover in compounds of this type must be largely inactivated by the resonance of the molecule; the perchlorate ion neutralises the normal thioxanthylium ion. It will be seen that this salt would show canonical forms similar in type to (II), (III), and (IV) and should therefore have similar properties to the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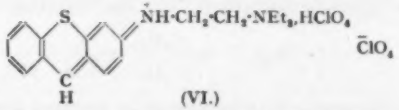

(VI.)

simple thioxanthylium salts. This has proved to be the case. We find that (V) and its 7-chloro-derivative form blue-black crystals which are readily hydrolysed by water, and the colour of their solutions in acetic acid slowly fades at room temperature. The first hydrol also gave an analogous chlorozincate, $XCl,HZnCl_3$, where X represents the cation of (V); this also formed blue-black crystals having similar physical properties to those of the perchlorates.

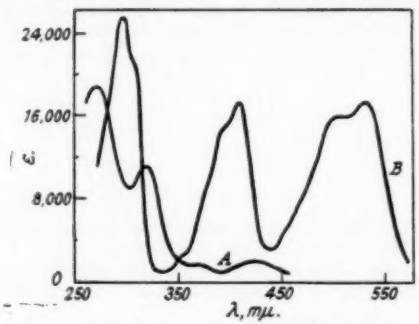
The 3-(2-diethylaminoethylamino)thioxanthones underwent similar reduction to give the hydrols, and the perchlorate hydrogen perchlorate salts had a similar composition (VI) to the 2-substituted analogues. Their properties were entirely different, however, for the 3-substituted salts formed crimson needles which were soluble in water without apparent hydrolysis; they

gave red solutions in glacial acetic acid which showed no fading after several days at room temperature. These crimson needles were furnished by the parent compound (VI) and by its 7-chloro- and 7-methyl derivative. All three cations furnished crimson chlorozincates, $XCl,HZnCl_2$, which had precisely analogous physical properties.

There is little doubt that the different colour and the greater stability of the 3-substituted salts arise from the greater degree of resonance which they can show. It will be clear that the resonance hybrid of these compounds will receive contributions not only from the canonical forms corresponding to (II), (III), and (IV), but also (and probably markedly) from the form (VI), and hence will be more stable than the 2-substituted analogues. This wider basis of resonance is confirmed by the absorption spectra (*A*) and (*B*) of the salts (V) and (VI), respectively. The curve (*A*) shows pronounced absorption in the ultra-violet and weak absorption in the visible region. In contrast the curve (*B*) shows a greater intensity of absorption, the bands are displaced to longer wave-lengths, and absorption in the visible region is strong.

These perchlorates and chlorozincates are thus in marked contrast to the chlorozincates of the unreduced 2- and 3-(diethylaminoethylamino)-xanthones and -thioxanthones, in which resonance of the above type is absent and in which therefore both amine groups can show their normal basic properties, so that the compounds form, for example, normal dihydrochlorides (see preceding paper).

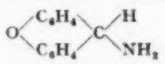
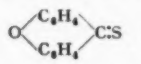
The preparation of 9-xanthylamine (VII) and of 9-thioxanthylamine, which are structurally akin to the corresponding hydrols, has received little attention in the past. We have investi-



(*A*) *Absorption spectrum of compound* (V) *in acetic acid.*
(*B*) ,, ,, ,, (VI) ,, ,,

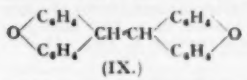
gated their synthesis in the hope that subsequent condensation with, for example, 2-diethylaminoethyl chloride would give the 2-diethylaminoethylamino side-chain in the 9-position. All previous compounds prepared in this investigation have had this side-chain in the same general plane as the tricyclic system; the new compounds would be fundamentally different in that the side-chain would be at right angles to this plane, and a correspondingly fundamental difference in therapeutic properties might possibly result.

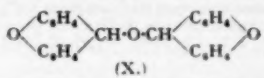
Treatment of xanthone or xanthione (VIII) with formamide (Leuckhart reaction) left these compounds unchanged, and the reduction of xanthone oxime was therefore investigated.

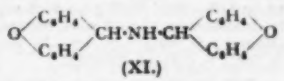
(VII.)   (VIII.)

This oxime cannot apparently be prepared directly by the action of hydroxylamine on xanthone (Fosse, *Compt. rend.*, 1906, **143**, 749), although Graebe and Röder (*Ber.*, 1899, **32**, 1678) record its preparation from xanthone anil. We find, however, that it can readily be prepared by the action of hydroxylamine on xanthione (VIII). Reduction of the oxime with zinc and acetic acid furnished only di-9-xanthyl (IX); reduction with sodium in ethanolic solution gave however the desired xanthylamine (VII) which was isolated as its acetate. The amine was also characterised by acetylation to *N*-9-xanthylacetamide, which Fosse (*loc. cit.*) had prepared by the interaction of xanthhydrol and acetamide, but had failed to hydrolyse to the xanthylamine. We have found the acetyl compound to be very resistant to alkaline hydrolysis, but it readily loses ammonia with acids.

9-Xanthylamine forms a well-defined crystalline hydrochloride, acetate, and picrate. It is however extremely susceptible to acid hydrolysis, and aqueous solutions of its salts slowly decompose at room temperature, and rapidly on being warmed, to give ammonia and a mixture of xanthhydrol and di-9-xanthyl ether (X). Even the picrate in warm ethanolic solution

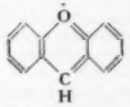

(IX.)

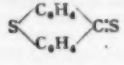

(X.)


(XI.)

rapidly gives ammonium picrate, whilst the hydrochloride when dissolved in concentrated hydrochloric acid gives xanthylium chloride.

Di-9-xanthylamine (XI) was prepared by the action of ammonia in ether on xanthylium chloride ferrichloride (XII). It is a crystalline compound, very susceptible to acid hydrolysis, and solutions in dilute hydrochloric or acetic acids consequently become milky.

(XII.)  $\bar{C}l,FeCl_3$


(XIII.)

We have attempted to prepare 9-thioxanthylamine (as VII) by converting thioxanthione (XIII) into thioxanthone oxime, and reducing the latter with sodium and ethanol, but the isolation of the pure amine by this method was difficult. When however thioxanthylium chloride ferrichloride (as XII) was treated with ammonia, both 9-thioxanthylamine and di-9-thioxanthylamine (as XI) were isolated. Both gave crystalline salts which underwent rapid hydrolysis with acids.

In view of the instability of all these amino-derivatives, the investigation of their condensation with alkyl halides was discontinued.

Experimental.

2-(2-*Diethylaminoethylamino*)*thioxanthylium Perchlorate Hydrogen Perchlorate.* (V).—2-(2-Diethylaminoethylamino)thioxanthone (0·2 g.) in ethanol (10 c.c.) was mixed with a solution of sodium hydroxide (0·6 g.) in water (0·5 c.c.), stirred under reflux on the water-bath, and zinc dust (0·25 g.) added in small portions during 15 minutes. 15 Minutes later the hot mixture was filtered, cooled, and diluted with water, and the resultant suspension extracted with ether. The ethereal extracts were washed with sodium hydroxide solution and dried (K_2CO_3), and the ether removed. The residual gum was dissolved in cold glacial acetic acid (10 c.c.), the green solution filtered, and a mixture of glacial acetic acid (40 c.c.) and 30% aqueous perchloric acid (0·6 c.c.) gradually added. The solution became Prussian blue, and the *perchlorate* separated as a blue-black crystalline powder (0·18 g.), m. p. 175° (decomp.) sintering at 160° (Found: C, 44·8; H, 4·4; N, 5·15. $C_{19}H_{22}N_2S,ClO_4.HClO_4$ requires C, 44·6; H, 4·7; N, 5·5%).

7-*Chloro*-2-(2-*diethylaminoethylamino*)*thioxanthylium Perchlorate Hydrogen Perchlorate.*—7-Chloro-2-(2-diethylaminoethylamino)thioxanthone (0·2 g.) was reduced and converted into the *perchlorate* exactly as in the foregoing experiment: it separated as a blue-black crystalline powder (0·19 g.), m. p. 180° (decomp.) sintering at 170° (Found: C, 42·0; H, 4·2; N, 5·3. $C_{19}H_{21}N_2ClS,ClO_4.HClO_4$ requires C, 41·8; H, 4·2; N, 5·1%).

2-(2-*Diethylaminoethylamino*)*thioxanthylium Chlorozincate.*—2-(2-Diethylaminoethylamino)thioxanthone (0·2 g.) was reduced as before. The residual gum was dissolved in glacial acetic acid (5 c.c.) and a 4% solution of zinc chloride in concentrated hydrochloric acid (2 c.c.) added, whereupon the grass-green solution became Prussian blue, and the *chlorozincate* separated as a metallic blue-black crystalline powder (0·21 g.), m. p. 190° (decomp.) (Found: C, 44·1; H, 4·45; N, 5·7. $C_{19}H_{22}N_2ClS,HZnCl_3$ requires C, 43·9; H, 4·7; N, 5·4%).

3-(2-*Diethylaminoethylamino*)*thioxanthylium Perchlorate Hydrogen Perchlorate* (VI).—3-(2-Diethylaminoethylamino)thioxanthone (0·2 g.) was reduced as in the foregoing experiments. The gummy product was isolated by extraction with ether and dissolved in glacial acetic acid (10 c.c.), the red solution filtered, and a solution of 30% perchloric acid (0·7 c.c.) in glacial acetic acid (60 c.c.) added. The monohydrated *perchlorate* slowly crystallised as a bright red powder, which was rapidly recrystallised from glacial acetic acid, giving glistening crimson plates (0·14 g.), m. p. 134—136° (sintering 130°) (Found: C, 43·6 H, 4·9; N, 5·4; Cl, 13·1; S, 6·2. $C_{19}H_{22}N_2S,ClO_4.HClO_4.H_2O$ requires C, 43·1; H, 5·0; N, 5·3; Cl, 13·4; S, 6·1%).

3-(2-*Diethylaminoethylamino*)-7-*methylthioxanthylium Perchlorate Hydrogen Perchlorate.*—3-(2-Diethylaminoethylamino)-7-methylthioxanthone (0·2 g.) was reduced as before, and the *perchlorate*, isolated in a similar way to the previous salt, separated as a crystalline scarlet powder (0·18 g.), m. p. 115° (decomp.) (Found: C, 45·9; H, 5·0; N, 5·55. $C_{20}H_{25}N_2S,ClO_4.HClO_4$ requires C, 45·7; H, 5·0; N, 5·3%).

7-*Chloro*-3-(2-*diethylaminoethylamino*)*thioxanthylium Perchlorate Hydrogen Perchlorate.*—7-Chloro-3-(2-diethylaminoethylamino)thioxanthone (0·2 g.), reduced and then treated as before, gave the *perchlorate*

as a scarlet powder (0·21 g.), m. p. 232 (decomp.) (Found: C, 42·2; H, 4·4; N, 5·2. $C_{19}H_{22}N_4ClS,ClO_4,HClO_4$ requires C, 41·8; H, 4·2; N, 5·1%).

3-(2-*Diethylaminoethylamino*)*thioxanthylium Chlorozincate*.—3-(2-Diethylaminoethylamino)thioxanthone (0·2 g.) in ethanol (10 c.c.) was reduced as in the foregoing experiment. The mixture was filtered, and a 2% solution of zinc chloride in dilute hydrochloric acid (20 c.c.) added. The red solid, m. p. 215—218° (0·27 g.), which separated was recrystallised from a 2% solution of zinc chloride in dilute hydrochloric acid and gave lustrous crimson needles (0·22 g.) of the *chlorozincate*, m. p. 230° (decomp.) (Found: C, 44·3; H, 4·9; N, 5·4; S, 6·3; Cl, 26·6. $C_{19}H_{23}N_3ClS,HZnCl_3$ requires C, 43·9; H, 4·7; N, 5·4; S, 6·2; Cl, 27·3%).

3-(2-*Diethylaminoethylamino*)-7-*methylthioxanthylium Chlorozincate*.—3-(2-Diethylaminoethylamino)-7-methylthioxanthone (0·2 g.) was reduced as before, and the *chlorozincate*, when similarly recrystallised, separated as crimson needles (0·2 g.), m. p. 238—240° (Found: C, 44·8; H, 5·25; N, 5·35. $C_{20}H_{25}N_3ClS,HZnCl_3$ requires C, 45·0; H, 4·9; N, 5·3%).

7-*Chloro*-3-(2-*diethylaminoethylamino*)*thioxanthylium Chlorozincate*.—7-Chloro-3-(2-diethylaminoethylamino)thioxanthone on reduction as before afforded the *chlorozincate*, which after the usual recrystallisation separated as scarlet needles, m. p. 234—235° (decomp.) (Found: C, 40·6; H, 4·5; N, 4·9. $C_{19}H_{22}N_3Cl_2S,HZnCl_3$ requires C, 41·1; H, 4·2; N, 5·1%).

Thiolacetic Acid.—The acid, prepared by Clarke and Hartman's method (*J. Amer. Chem. Soc.*, 1924, **46**, 1731), and carefully fractionated through a long column, was obtained as a colourless, highly refracting liquid (b. p. 90—92°) with a pungent unpleasant smell. The iodine equivalent (ε) of the product was determined by Klason and Carlson's method (*Ber.*, 1906, **39**, 738) (Found: ε, 87. Calc.: ε, 76).

Xanthione.—Xanthone (15 g.) and thionyl chloride (15 c.c.) were heated on a water-bath for 4 hours. The clear red solution was evaporated to dryness in a vacuum, the residue dissolved in dry benzene (90 c.c.) and cooled, and thiolacetic acid (22·5 g.) added dropwise in a stream of nitrogen. The dark-brown product was heated on the water-bath for 4 hours, the solution evaporated to half-bulk and cooled, and the solid collected and then recrystallised from benzene giving xanthione as deep-red needles (7·5 g.), m. p. 152—154°. Schönberg (*Ber.*, 1928, **61**, 1382) records m. p. 156°.

Xanthone Oxime.—Finely powdered hydroxylamine hydrochloride (2·5 g.) was added in small portions to a solution of xanthione (2·5 g.) in warm dry pyridine (25 c.c.). The dark-green solution was heated at 100° for 2 hours; the colour faded and hydrogen sulphide was evolved. The product was cooled and poured into water, and the oxime separated as an oil which rapidly solidified (2·35 g.); recrystallisation from benzene gave glistening white needles, m. p. 160—161° (Found: C, 74·2; H, 4·3; N, 6·5. Calc. for $C_{13}H_9O_2N$: C, 73·9; H, 4·3; N, 6·6%). Graebe and Röder (*loc. cit.*) record m. p. 164°.

The oxime was soluble in concentrated hydrochloric acid, but insoluble in dilute aqueous sodium hydroxide. A solution in concentrated sulphuric acid was colourless, and showed no fluorescence.

Reduction of Xanthone Oxime with Zinc in Acetic Acid.—Xanthone oxime (1·5 g.) was stirred under reflux with glacial acetic acid (20 c.c.) and water (1 c.c.), and zinc dust (3·5 g.) added during 15 minutes. The solution became brown, and a white crystalline solid separated. The mixture was heated under reflux for 1 hour and cooled, and the solid collected and extracted with ethyl acetate (Soxhlet). The extracts were evaporated to dryness, and the residue (0·9 g.) recrystallised from glacial acetic acid giving long white needles, m. p. 204—205°, identical with di-9-xanthyl prepared by the reduction of xanthhydrol (Wanscheidt and Moldavski, *Ber.*, 1930, **63**, 1368).

9-*Xanthylamine Acetate*.—Xanthone oxime (1·0 g.) was heated under reflux with alcohol (40 c.c.) whilst sodium (4·0 g.; small shavings) was added during 20 minutes. The product was cooled, ice added, and the mixture extracted with ether. The ethereal solution was washed with water, and shaken with cold 10% acetic acid (2 × 5 c.c.). The united acid extracts were cooled to 0° and scratched to induce crystallisation; the *amine acetate* separated as a white solid (0·5 g.), m. p. 150—151° (decomp.). A portion, recrystallised from benzene (containing a trace of acetic acid), gave white needles (Found: C, 69·5; H, 5·8; N, 5·5. $C_{13}H_{11}ON,C_2H_4O_2$ requires C, 70·0; H, 5·9; N, 5·5%).

The *amine picrate*, prepared by adding ethanolic picric acid to a solution of the acetate (0·1 g.) in ethanol (3 c.c.), separated in yellow needles, m. p. 200—202° (Found: C, 53·7; H, 3·5; N, 13·4. $C_{13}H_{11}ON,C_6H_3O_7N_3$ requires C, 53·5; H, 3·3; N, 13·1%).

A hot ethanolic solution of the picrate slowly deposited yellow crystals, m. p. 290° (decomp.), which showed no depression of m. p. on admixture with authentic ammonium picrate (Found: C, 30·1; H, 2·5; N, 23·2. Calc. for $C_6H_6O_7N_4$: C, 29·3; H, 2·5; N, 22·8%).

9-*Xanthylamine*.—Dilute ammonia solution was added to a suspension of 9-xanthylamine acetate (0·16 g.) in water (5 c.c.). The *base* separated as an oil which slowly solidified and, when recrystallised from petroleum (b. p. 40—60°), gave long white needles, m. p. 59—61° (Found: C, 79·6; H, 5·6; N, 6·9. $C_{13}H_{11}ON$ requires C, 79·2; H, 5·6; N, 7·1%). A solution in concentrated sulphuric acid was yellow with an intense-green fluorescence.

The *hydrochloride*, prepared by adding cold saturated alcoholic hydrogen chloride (1 c.c.) to an ice-cold solution of the base (0·1 g.) in ethanol (1·5 c.c.), separated as white needles (0·07 g.), m. p. 355° (decomp.) (Found: C, 67·3; H, 5·6; N, 6·1. $C_{13}H_{11}ON,HCl$ requires C, 66·8; H, 5·2; N, 6·0%). A solution of the hydrochloride (0·2 g.) in cold water (5 c.c.) was gently warmed to 100°; a white crystalline solid (0·15 g.), m. p. 135—145°, separated. It contained no nitrogen, and was evidently impure di-9-xanthyl ether (Found: C, 82·9; H, 5·1. Calc. for $C_{26}H_{18}O_3$: C, 82·5; H, 4·8%).

N-9-*Xanthylacetamide*.—Xanthylamine (0·1 g.) and acetic anhydride (0·1 g.) were heated at 100° for 30 minutes. The product was cooled and diluted with water, and the solid was collected and recrystallised from 80% dioxan–water giving long white needles, m. p. 240—242° undepressed on admixture with

authentic *N*-9-xanthylacetamide prepared from xanthhydrol (Fosse, *loc. cit.*; Phillips and Pitt, *J. Amer. Chem. Soc.*, 1943, **65**, 1355).

Xanthylium Chloride Ferrichloride (XII).— Xanthhydrol (1·0 g.) was dissolved in dry ether (10 c.c.), saturated with dry hydrogen chloride at 0°, and an ethereal solution of anhydrous ferric chloride (1 g.) added. The double salt was precipitated as a yellow solid which was collected, washed with ether, and dried in a vacuum; it (0·8 g.) had m. p. 190° (sintering at 185°). Gomberg and Cone (*loc. cit.*) record m. p. 193°.

Di-9-xanthylamine.— A suspension of the ferrichloride (2·0 g.) in ether (30 c.c.) was saturated with dry ammonia at 0°. The filtered product was evaporated, leaving a gum which crystallised on treatment with petroleum to give *di-9-xanthylamine* (0·22 g.); crystallisation from ethanol afforded glistening needles, m. p. 154° (Found: C, 82·7; H, 5·3; N, 4·2. $C_{26}H_{19}O_2N$ requires C, 82·7; H, 5·1; N, 3·7%). A solution of the base in concentrated sulphuric acid was yellow and showed an intense green fluorescence.

Thioxanthone.—This compound was prepared by the action of concentrated sulphuric acid on a suspension of *o*-mercaptobenzoic acid in benzene (Davis and Smiles, *J.*, 1910, **97**, 1296).

Thioxanthione.—Thioxanthone (9·3 g.) and thionyl chloride (9·3 c.c.) were heated on a water-bath for 4 hours. The clear dark-red solution was evaporated to dryness in a vacuum, the residue dissolved in dry benzene (130 c.c.), and thiolacetic acid (16·3 g.) dropped in at 0°, under a nitrogen atmosphere. The product was heated on the water-bath for 5 hours, filtered, and evaporated to small bulk, whereupon the thioketone was slowly deposited as a lustrous brown solid (6·9 g.), m. p. 160—168°. Schönberg (*loc. cit.*) records m. p. 168°.

Thioxanthone Oxime.—The crude thioxanthione (6·9 g.) was dissolved in warm pyridine (70 c.c.), cooled, and powdered hydroxylamine hydrochloride (7 g.) gradually added. The mixture was warmed on the water-bath for 1 hour, cooled, and poured into water, and the solid (7·7 g.) collected. The dry material was ground in a mortar with ethanol (100 c.c.) and filtered, and the filtrate diluted with water; the *oxime* was precipitated as a white solid which crystallised from petroleum (b. p. 80—100°) in pale-yellow needles (2·5 g.), m. p. 194—196° (sintering at 180°) (Found: C, 68·7; H, 4·3; N, 6·1. $C_{13}H_9ONS$ requires C, 68·7; H, 4·0; N, 6·2%). A solution of the oxime in concentrated sulphuric acid was yellow and non-fluorescent.

Thioxanthhydrol.—Thioxanthone (5 g.) suspended in ethanol (35 c.c.) was reduced by shaking with sodium amalgam exactly as in the preparation of xanthhydrol (*Org. Synth.*, Coll. Vol. I, p. 554). The hydrol was isolated as a white solid (4·2 g.), m. p. 100—102°. Hilditch and Smiles (*loc. cit.*) record m. p. 103—104°.

Thioxanthylium Chloride Ferrichloride.—This was prepared precisely as the xanthylium analogue and obtained as an orange-red solid, which was washed with ether and dried in a vacuum; it (6·5 g.) had m. p. 192—195°. Hilditch and Smiles (*loc. cit.*) record m. p. 193—194°.

Di-9-thioxanthylamine.—The above salt (6·5 g.) was suspended in ether (200 c.c.), and saturated with dry ammonia at 0°. The mixture was filtered and the ethereal filtrate concentrated to *ca.* 10 c.c., whereupon the *amine* (1·1 g.) was deposited; it separated from ethanol in crystals, m. p. 167—168° (Found: C, 76·5; H, 4·6; N, 3·5. $C_{26}H_{19}NS_2$ requires C, 76·2; H, 4·7; N, 3·4%). A solution in concentrated sulphuric acid was faintly pink, and showed a strong yellow fluorescence.

9-*Thioxanthylamine Acetate.*—Evaporation of the ethereal mother-liquors, after removal of the secondary amine in the foregoing experiment, yielded a gum (1·0 g.) which solidified on treatment with 10% acetic acid at 0° to give *thioxanthylamine acetate* (0·7 g.) which crystallised from benzene (containing a trace of acetic acid) as small white needles, m. p. 152° (sinters at 135°) (Found: C, 65·9; H, 5·6; N, 5·15. $C_{13}H_{11}NS,C_2H_4O_2$ requires C, 65·9; H, 5·55; N, 5·1%).

An aqueous solution of the salt rapidly became turbid when warmed. With concentrated sulphuric acid the salt gave a similar colour reaction to the corresponding secondary amine.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, October 21st*, 1950].

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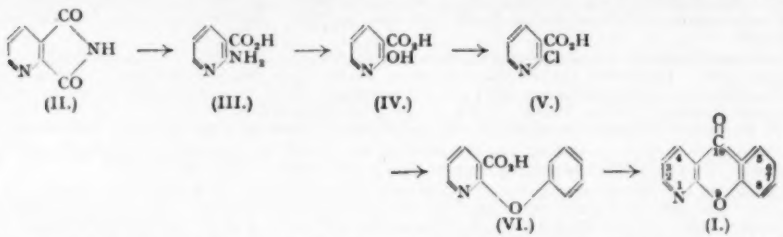
164. *Xanthones and Thioxanthones. Part III. The Synthesis of 9-Oxa-1-aza-anthrone (4-Azaxanthone).*

By FREDERICK G. MANN and J. HEDLEY TURNBULL.

The synthesis of 9-oxa-1-aza-anthrone is described as part of a general investigation of the various isomeric aza-derivatives of xanthone and thioxanthone.

THE replacement of one of the benzene rings in xanthone by a pyridine ring can theoretically give rise to four isomeric aza-9-oxa-anthrones. These novel heterocyclic systems may prove of considerable chemical and therapeutic interest, and we are now investigating their syntheses and properties. The present communication records briefly the synthesis of one of these compounds, namely 9-oxa-1-aza-anthrone (4-azaxanthone) (I).

2-Aminonicotinic acid (III) was prepared by Sucharda's method (*Ber.*, 1925, **58**, 1728), 8-hydroxyquinoline being converted into quinolinimide (II). This imide, when subjected to the Hofmann reaction, gave a mixture of 2-aminonicotinic acid (III) and 3-aminopicolinic



(II.) (III.) (IV.) (V.) (VI.) (I.)

acid. The former could be readily isolated by virtue of its lower solubility, and on treatment with nitrous acid gave 2-hydroxynicotinic acid (IV) (Philips, *Annalen*, 1895, **288**, 253) which in turn, with phosphorus pentachloride, yielded 2-chloronicotinic acid (V) (Wiedel and Strache, *Monatsh.*, 1886, **7**, 295). The sodium salt of this acid condensed with sodium phenoxide to give 2-phenoxynicotinic acid (VI), which on being heated with phosphorus oxychloride underwent cyclisation to (I); for success in the last two stages of this synthesis, however, very careful control of the conditions was essential. The oxa-aza-anthrone after sublimation formed fine, white needles, slightly soluble in water and readily soluble in strong mineral acids. Its pale yellow solution in concentrated sulphuric acid showed a faint green fluorescence.

Experimental.

2-Aminonicotinic Acid (III).—A solution of sodium hypochlorite (148 g.), prepared by passing chlorine (11·4 g.) into a mixture of sodium hydroxide (14·7 g.), water (27 c.c.), and ice (95 g.), was added to a solution of the imide (II) (23 g.) in cold 10% aqueous sodium hydroxide solution. The mixture was warmed to 80°, maintained at that temperature for 30 minutes, cooled, and acidified with 50% sulphuric acid (90 g.) and glacial acetic acid (*ca.* 5 c.c.); the aminonicotinic acid (5·7 g.) separated, and was recrystallised from water forming glistening pale-yellow plates (4 g.), m. p. 293° (decomp.). Philips (*loc. cit.*) records m. p. 310° (decomp.). The mother-liquors from the acidification contained 3-aminopicolinic acid which could be isolated as the copper salt (Sucharda, *loc. cit.*).

2-Hydroxynicotinic Acid (IV).—2-Aminonicotinic acid (4 g.) was dissolved in hot 10% sulphuric acid (32 c.c.), water (120 c.c.) added, and a solution of sodium nitrite (2 g.) in water (20 c.c.) run in at 40—50°. The clear solution was heated at 100° for 30 minutes and then cooled; the hydroxy-acid separated in long, white needles (2·5 g.), m. p. 255°.

2-Chloronicotinic Acid (V).—A mixture of the hydroxy-acid (1·0 g.), phosphorus oxychloride (0·5 c.c.), and phosphorus pentachloride (2·5 g.) was heated gradually to 140—145°. The clear melt was maintained at 140° for 10 minutes, cooled, and poured into ice-water, and the precipitated solid recrystallised from hot water giving pale yellow plates of the chloro-acid (V) (0·8 g.), m. p. 189° (decomp.). Wiedel and Strache (*loc. cit.*) record m. p. 193°.

2-Phenoxynicotinic Acid (VI).—2-Chloronicotinic acid (0·5 g.) and phenol (1 g.) were added in turn to methanol (4 c.c.) in which sodium (0·15 g.) had previously been dissolved. The mixture was evaporated to dryness at 100°, and the residue slowly heated to 170°, whereupon the mass melted and effervesced. The melt was cooled, dissolved in water, and extracted with ether, and the aqueous solution acidified with acetic acid. The phenoxynicotinic acid separated as a white solid (0·53 g.), m. p. 177—179°, which separated from dilute acetic acid in slender crystals, m. p. 179—180°, which were completely soluble in sodium hydrogen carbonate solution (Found: C, 67·1; H, 4·3; N, 6·8. $C_{12}H_9O_3N$ requires C, 67·0; H, 4·2; N, 6·5%).

9-Oxa-1-aza-anthrone (I).—A mixture of (VI) (100 mg.) and phosphorus oxychloride (2 c.c.) was heated under reflux for 30 minutes. The green solution was cooled and diluted with petroleum (b. p. 40—60°), and the precipitated solid collected, washed with water, dried (20 mg.), and sublimed at 170°/0·5 mm. The *oxa-aza-anthrone* was obtained as a white sublimate (15 mg.) which crystallised from dilute acetic acid in hair-like white needles, m. p. 182—183° (Found: C, 73·4; H, 3·7; N, 7·3. $C_{12}H_7O_2N$ requires C, 73·1; H, 3·6; N, 7·1%). The low solubility of this compound in cold dilute acetic acid indicates that it has only weakly basic properties.

University Chemical Laboratory, Cambridge. [*Received, October 21st*, 1950.]

165. *Researches on Acetylenic Compounds. Part XXX. Catalytic and Inhibitory Effects in the Reppe Carboxylation Reaction.*

By E. R. H. Jones, T. Y. Shen, and M. C. Whiting.

The extension of the Reppe carboxylation reaction to acetylenic halides has been investigated. 1-Iodoacetylenes are reduced by nickel carbonyl to the corresponding acetylenes, and simultaneously inhibit the normal reaction which the latter usually undergo with nickel carbonyl. Vinylacetylenes can be induced to react with nickel carbonyl by adding pyridine; dimeric products are obtained. Some complex salts obtained from nickel carbonyl are described.

During a systematic exploration of the Reppe carboxylation reaction, several types of acetylenic compounds have been treated with nickel carbonyl (Jones, Shen, and Whiting, *J.*, 1950, 230; 1951, 48). Some halogeno-acetylenic compounds have now been submitted to the reaction.

When 1-iodohex-1-yne was treated with nickel carbonyl under the usual conditions (*i.e.*, in aqueous-ethanolic acetic acid at about 70°) no exothermic reaction occurred, although a brown colour developed. No acidic product was obtained, but distillation of the neutral fraction gave, rather unexpectedly, an appreciable yield of the parent hex-1-yne, in addition to 20% of unchanged iodohexyne. In the same way, 1-iodo-2-phenylacetylene gave a 44% yield of phenylacetylene, 20% of the starting material being recovered. Presumably, the nickel carbonyl in these reactions is behaving as a reducing agent:

$$2R{\cdot}C{\equiv}C{\cdot}I + 2Ni(CO)_4 + 2AcOH \longrightarrow 2R{\cdot}C{\equiv}CH + Ni(OAc)_2 + NiI_2 + 8CO$$

This reduction proceeds slowly, whereas the carboxylation of hex-1-yne and phenylacetylene by nickel carbonyl normally occurs very rapidly, after a brief induction period, in these conditions. In order to account for the surprising fact that the acetylenic hydrocarbons produced in these reactions do not react subsequently with the nickel carbonyl present, it seemed reasonable to postulate the operation of some inhibiting influence.

It was at first thought possible that free iodine, which is very readily liberated from iodoacetylenic compounds, might be acting as an inhibitor. However, in a control experiment in which phenylacetylene and a little iodine were treated with nickel carbonyl in aqueous-ethanolic acetic acid at 70°, the colour of the iodine was rapidly discharged as soon as the addition of the carbonyl began, and a normal reaction then ensued. The only difference from the usual results was the esterification of an abnormally large proportion of the atropic acid formed, presumably because of the catalytic effect of the nickel iodide present. It therefore appeared that the iodoacetylenes themselves might be capable of inhibiting the Reppe carboxylation; if so, and if their reduction proceeds to completion, the use of a large excess of nickel carbonyl should allow the normal vigorous carboxylation reaction to occur. This was found to be the case. When iodophenylacetylene was treated under the standard conditions at 70° with a large excess of nickel carbonyl, no detectable exothermic reaction occurred during 20 minutes; the usual, sudden, highly exothermic reaction then took place; working up gave a trace of atropic acid and a 32% yield of ethyl atropate (in this instance quite a large quantity of nickel iodide, evidently a good esterification catalyst, was present). No phenylacetylene or iodophenylacetylene could be isolated.

This evidence of inhibition by an acetylenic compound suggested the hypothesis that the "inert" acetylenic compounds referred to earlier (*locc. cit.*; see also following paper), which do not react vigorously with nickel carbonyl, may owe this inability to react to a self-inhibitory effect. If so, they should be able to hinder the carboxylation of typical "reactive" acetylenes. Therefore, mixtures, in various ratios, of a typical "inert" acetylene, 1-ethynyl*cyclo*hexyl acetate "(A)," and one which reacts normally, hex-1-yne "(B)," were treated with nickel carbonyl under the standard conditions. The results are tabulated below:

Molar ratio, B : A.	Exothermic reaction.	A recovered, %.	B recovered.	$Bu{\cdot}C(CO_2H){=}CH_2$ yield, %.
1	None	60	Yes	0
4	None	0	Yes	0
20	After long induction	0	None	27
A not present	Normal	—	None	35

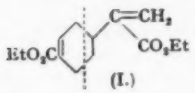
The evidence for the existence of such an inhibitory effect is convincing but it is impossible at this stage to estimate its importance and generality.

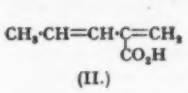
The behaviour of 1-bromohex-1-yne on treatment with nickel carbonyl was quite different from that of the iodo-compound. No exothermic reaction occurred, no hex-1-yne was formed and, despite the formation of much dark polymeric material, the bromo-compound was recovered in 46% yield. No acidic product was isolated.

Attempts were made to apply the reaction to various other types of acetylenic halides. 1 : 4-Dichlorobut-2-yne underwent an exothermic reaction on treatment with nickel carbonyl, but distillation of the reaction product resulted in decomposition. 1-Bromopent-4-yne, however, reacted smoothly and gave the expected α-methylenic acid in 22% yield, together with about 18% of the corresponding ester.

Because of the general similarity between the properties of alkyl halides and toluene-*p*-sulphonates, attempts were made to effect reactions between nickel carbonyl and the toluene-*p*-sulphonates of but-2-yne-1 : 4-diol, but-3-yn-1-ol, and pent-4-yn-1-ol. Unfortunately, rapid hydrolysis occurred instead in every case; no exothermic reactions were observed and a light-green precipitate of nickel toluene-*p*-sulphonate was formed in considerable quantity. In the case of pent-4-yn-1-yl toluene-*p*-sulphonate, however, isolation of the acidic fraction did give a small (1·5%) yield of a crystalline product which analysed as expected for the α-methylenic acid.

The failure of several substituted vinylacetylenes to undergo the Reppe carboxylation reaction under the normal conditions has already been described (*locc. cit.*). On the other hand, Reppe (" Acetylene Chemistry," translation, Meyer, 1949, p. 158) states that vinylacetylene reacts with nickel carbonyl in ethanol containing hydrochloric acid to give a dimer of


(I.)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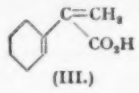
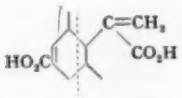
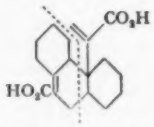

(III.)

(IV.)




(V.)

the expected buta-1 : 3-diene-2-carboxylic acid, and suggests a possible structure (I) for it. An attempt to induce substituted vinylacetylenes to react essentially under our standard conditions has now been made by adding pyridine, which decomposes nickel carbonyl rapidly in acetic acid solution and might thus be expected to initiate the reaction. With the typical examples, pent-3-en-1-yne and 1-ethynyl*cyclo*hexene, no exothermic reactions ensued on slow addition of nickel carbonyl to their solutions in aqueous ethanolic acetic acid, containing one molecular proportion of pyridine, at 70°; but subsequent isolation gave appreciable quantities of acid. This in each case was separable into a crystalline fraction (m. p.s 230—232° and 251—252°, respectively) and a liquid portion which rapidly polymerised and was not investigated further. The crystalline acids gave analytical values expected for (II) and (III) respectively, but their physical properties suggested that they were dimeric, and in the case of the acid prepared from pent-3-en-1-yne this was proved by determination of the molecular weight of the dimethyl ester. Reppe's proposed structure (I) (the evidence upon which it was based has not yet been published) implies a Diels–Alder type of dimerisation, eminently plausible for primary products such as (II) and (III). If this interpretation is valid for the cases investigated, the products, (IV) and (V), should show the light absorption typical of αβ-unsaturated acids and esters; such is indeed the case. The product from 1-ethynyl*cyclo*hexene exhibits a maximum at a longer wave-length than that from pent-3-en-1-yne, as would be expected. There is therefore *prima facie* evidence for the correctness of the formulæ assigned, although various other possibilities cannot be excluded.

The results of adding pyridine to the reaction mixture in the cases of various other types of acetylenes were less remarkable. Vinylacetylene itself rather unexpectedly failed to give a crystalline product, although a certain amount of acidic material, which rapidly polymerised, was formed. The " inert " tertiary acetate, 1-ethynyl*cyclo*hexyl acetate, still gave the expected product in small yield (7%, as against 3% without pyridine). In the case of iodophenylacetylene, addition of pyridine did not alter the course of the reaction: slow reduction took

place, followed (provided that sufficient nickel carbonyl was used) by rapid carboxylation of the phenylacetylene, and isolation of the products gave atropic acid and ester in 35% total yield. When phenylacetylene was treated with nickel carbonyl in the presence of pyridine the carboxylation reaction began without the normal induction period, and atropic acid was obtained in the usual yield, *i.e.*, 49%. It was also possible to effect the carboxylation of phenylacetylene (yield, 45%) when a mixture of pyridine, acetic acid, and water was used as solvent, in spite of the fact that this mixture rapidly decomposes the carbonyl.

It was noted, in the experiments with phenylacetylene just described, that when the reaction mixture cooled a deep-green solid separated. This appeared to be a complex salt of atropic acid, since the latter was precipitated on acidification of its aqueous solution. An apparently analogous salt was obtained by adding nickel carbonyl to an aqueous-ethanolic acetic acid solution of pyridine; it gave analytical figures for a dipyridine nickel diacetate dihydrate. The atropate, however, gave analytical values which could only be explained by assuming a solvate with one molecule of ethanol. Co-ordination complexes of nickel with two molecules of pyridine have not been described previously, but salts of copper containing only two amine molecules have recently been prepared (Broom, Ralston, and Thornton, *J. Amer. Chem. Soc.*, 1946, **68**, 67). It is of course possible that the organic acids are weakly co-ordinated to the nickel atom in these substances; in any case, their chemistry might repay investigation.

Experimental.

Reaction of 1-*Iodohex*-1-*yne with Nickel Carbonyl.*—To a solution of 1-iodohex-1-yne (10 g.; Grignard and Perrichon, *Ann. Chim.*, 1926, **5**, 5) in ethanol (20 c.c.), acetic acid (3 c.c.), and water (1 c.c.), nickel carbonyl (3 c.c.) in ethanol (7 c.c.) was added slowly at 70°. No exothermic reaction was observed, and the reaction mixture was kept at 75—80° for about 30 minutes. Removal of excess of nickel carbonyl by co-distillation with ether and isolation of the neutral fraction (care being taken to remove alcohol by washing and to avoid loss of volatile material), followed by distillation, gave (*a*) hex-1-yne (containing some alcohol) (2·5 g., ~60%), b. p. 65—72°, n_D^{19} 1·3853, and (*b*) recovered iodohexyne (2 g., 20%). Fraction (*a*) was recognised by its physical constants (pure hex-1-yne has b. p. 71°, n_D^{24} 1·3969), its odour, and its insoluble silver derivative. No appreciable acid fraction was present.

Reaction of Iodophenylacetylene with Nickel Carbonyl.—(*a*) To a solution of iodophenylacetylene (10·8 g.; prepared by the method of Grignard and Perrichon, *loc. cit.*) in ethanol (25 c.c.), water (1 c.c.), and acetic acid (3 c.c.), nickel carbonyl (5 c.c.) in ethanol (10 c.c.) was added slowly at 75—80°. The solution became dark brown, but no exothermic reaction was observed. After 20 minutes' heating isolation gave a negligible acidic fraction; the neutral fraction yielded phenylacetylene (2·1 g.; 44%), b. p. 81—83°/100 mm., n_D^{20} 1·5420 (Bourguel, *Ann. Chim.*, 1924, **3**, 229, gives b. p. 142—143°, n_D^{20} 1·548), and unchanged iodophenylacetylene (2·0 g., 18%), b. p. 123°/18 mm., n_D^{20} 1·6648. (Wieland and Fischer, *Annalen*, 1925, **446**, 67, give b. p. 114—116°/12 mm.)

(*b*) In a similar experiment in which 5·7 g. of iodophenylacetylene, 5 c.c. of nickel carbonyl, and 4 c.c. of acetic acid were employed, a period (10 minutes) when no conspicuous exothermic reaction occurred was followed by a sudden rise in temperature. Isolation then gave a trace of atropic acid, m. p. 102—104°, undepressed on admixture with an authentic specimen, and ethyl atropate (1·4 g., 32%), b. p. 67—71°/0·2 mm., n_D^{22} 1·526 (Auwers and Eisenlohr, *J. pr. Chem.*, 1911, **84**, 89, give b. p. 120·2—120·4°/14 mm., n_D^{16} 1·5260). The latter was characterised by alkaline hydrolysis (albeit in poor yield, as was usually the case) to atropic acid, m. p. 101—104°, undepressed on admixture with an authentic specimen (m. p. 106—107°).

(*c*) In a similar experiment in which phenylacetylene (7·7 g.), pyridine (2 c.c.), nickel carbonyl (5·5 c.c.), acetic acid (5 c.c.), water (1 c.c.), and ethanol (30 c.c.) were employed, no exothermic reaction occurred on addition of the carbonyl, although a deep green coloration was observed initially. After half the carbonyl had been added the solution became brown and 20 minutes after the commencement of the addition an exothermic reaction occurred suddenly. Atropic acid (0·18 g., 3%), m. p. 104—105°, and ethyl atropate (1·85 g., 32%), b. p. 85°/0·3 mm., n_D^{22} 1·5236, were obtained.

5-Bromopent-1-*ene*-2-*carboxylic Acid and its Ethyl Ester.*—5-Bromopent-1-yne (9·1 g.; Eglinton and Whiting, *J.*, 1950, 3650), acetic acid (3 c.c.), water (1 c.c.), and ethanol (25 c.c.) were treated with nickel carbonyl (3 c.c.) in ethanol (10 c.c.) at 70°. An exothermic reaction occurred; removal of excess of the carbonyl and isolation of the acidic and neutral fractions gave respectively the *acid* (2·6 g., 22%), b. p. 85°/0·05 mm., n_D^{20} 1·5047 (Found: C, 38·75, 38·5; H, 4·8, 4·8; Br, 40·5. $C_5H_9O_2Br$ requires C, 37·35; H, 4·7; Br, 41·4%), and the *ethyl* ester (2·5 g., 18%), b. p. 53°/0·02 mm., 113°/16 mm., n_D^{21} 1·4751 (Found: C, 43·9, 44·5; H, 6·05, 6·0; Br, 35·2. $C_9H_{13}O_2Br$ requires C, 43·45; H, 5·9; Br, 36·1%). Treatment of the acid with thionyl chloride and then with *p*-toluidine gave the corresponding *p-toluidide*, which formed plates, m. p. 78°, from benzene–light petroleum (Found: C, 55·85; H, 5·55; N, 4·85, 5·05; Br, 26·8. $C_{12}H_{14}ONBr$ requires C, 55·3; H, 5·7; N, 4·95; Br, 28·3%). No reasonable explanation for the consistently inaccurate analyses of these compounds, which appeared to be pure, can be suggested.

Toluene-p-*sulphonate of* 5-*Hydroxypent*-1-*ene*-2-*carboxylic Acid.*—A solution of pent-4-yn-1-yl toluene-*p*-sulphonate (12 g.; Eglinton and Whiting, *loc. cit.*) in acetone (2 c.c.), acetic acid (3 c.c.), and water (1 c.c.) was heated under reflux at 55—60° while a solution of nickel carbonyl (3 c.c.) in acetone (10 c.c.) was added during 15 minutes. A green precipitate slowly formed; no exothermic reaction occurred. Separation of the acidic fraction, after the removal of excess of carbonyl, gave an oil which

partly solidified; crystallisation from benzene–light petroleum gave the *acid toluene*-p-*sulphonate* (0·2 g., 1·5%) as prisms, m. p. 85° (Found: C, 55·0; H, 5·8. $C_{19}H_{16}O_5S$ requires C, 54·95; H, 5·65%).

Reppe Carboxylation of Pent-2-en-4-yne.—A solution of pent-2-en-4-yne (4·6 g.; Eglinton and Whiting, *loc. cit.*), acetic acid (5 c.c.), water (3 c.c.), pyridine (5 c.c.), and ethanol (35 c.c.) was treated slowly with nickel carbonyl (4 c.c.) at 65—70°. The acidic fraction of the product partly solidified, and was separated into an oil (2·1 g.) which rapidly polymerised and was not investigated further, and a solid, m. p. 228—230° (1·2 g., 16%), which on recrystallisation from aqueous methanol gave the dimeric *acid* (IV?) as prisms, m. p. 230—232° [Found: C, 64·5; H, 7·25. $(C_6H_8O_2)_n$ requires C, 64·3; H, 7·2%]. Light absorption: End absorption, $\varepsilon = 12{,}000$ at 2160 A., assuming the doubled formula. The *methyl* ester, obtained with diazomethane had b. p. 115° (bath-temp.)/10^{-5} mm., n_D^{18} 1·4986 [Found: C, 66·3; H, 7·55; *M* (ebullioscopic), 241. $(C_7H_{10}O_2)_2$ requires C, 66·6; H, 8·0%; *M*, 252].

Reppe Carboxylation of 1-*Ethynylcyclohex*-1-*ene.*—Ethynylcyclohexene (5·4 g.; see Hamlet, Henbest, and Jones, forthcoming publication, for an improved method of preparation), water (2 c.c.), pyridine (5 c.c.), acetic acid (4 c.c.), and ethanol (20 c.c.) were treated slowly with nickel carbonyl (4 c.c.) in ethanol (10 c.c.) at 70°. No exothermic reaction occurred; the acidic fraction partly solidified, yielding, after crystallisation from ethyl acetate, the presumably dimeric *acid* (V?) (1·15 g., 15%), m. p. 251—252° [Found: C, 71·25; H, 7·75. $(C_9H_{12}O_2)_2$ requires C, 71·05; H, 7·95%]. Light absorption: Max., 2230—2260 A., $\varepsilon = 9400$.

Complex Salts from Nickel Carbonyl.—(*a*) On treatment of a solution of phenylacetylene and pyridine in aqueous ethanolic acetic acid with nickel carbonyl an exothermic reaction occurred immediately. When the solution was freed from excess of the carbonyl by co-distillation with ether and allowed to cool, deep green crystals separated. Recrystallisation from ethanol containing a few drops of pyridine gave a complex *salt* as bluish-green prisms, m. p. 150—154° [Found: C, 64·35; H, 5·0; N, 5·15. $C_{36}H_{32}O_8N_2Ni$, *i.e.*, $Ni(O{\cdot}CO{\cdot}CPh{:}CH_2)_2,2C_5H_5N,C_2H_5{\cdot}OH$ requires C, 64·65; H, 5·4; N, 5·0%]. Heating above 100° at 10^{-5} mm. converted it into grass-green prisms which decomposed, without melting, at 220°. Both this substance and the complex salt gave an immediate precipitate of atropic acid when their aqueous solutions were acidified.

(*b*) On addition of nickel carbonyl to a solution of pyridine in aqueous-ethanolic acetic acid the solution became warm and rapidly became green; on concentration it deposited blue crystals. Recrystallisation from aqueous ethanol containing a little pyridine gave greenish-blue prisms, m. p. 140—141° [Found: C, 45·6; H, 5·5; N, 7·3. $C_{10}H_{20}O_6N_2Ni$, *i.e.*, $Ni(O{\cdot}OC{\cdot}CH_3)_2,2C_5H_5N,2H_2O$ requires C, 45·3; H, 5·4; N, 7·55%].

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THE UNIVERSITY, MANCHESTER, 13. [*Received, November 15th*, 1950.]

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166. *Researches on Acetylenic Compounds. Part XXXI. Some Qualitative and Quantitative Aspects of the Reppe Carboxylation Reaction.*

By E. R. H. JONES, T. Y. SHEN, and M. C. WHITING.

As a necessary preliminary to an investigation of the mechanism of the Reppe carboxylation reaction, the degree of specificity of the various participants in the reaction has been investigated, and the stoicheiometry of the process examined.

THIS reaction was originally formulated by Reppe (see Copenhaver and Bigelow, "Acetylene Chemistry," Reinhold, 1949, p. 252) as follows:

$$4RC{\equiv}CR + Ni(CO)_4 + 2HX + 4HY \longrightarrow 4H{\cdot}CR{=}CR{\cdot}CO_2Y + NiX_2 + H_2$$

where HX and HY are respectively an acid, and a compound containing active hydrogen, *e.g.* ethanol. In preliminary investigations (Part XXII; Jones, Shen, and Whiting, *J.*, 1950, 230; *q.v.* for references to earlier work) certain anomalies were encountered, and it was therefore concluded that speculation about the mechanism of the reaction was useless until more information was available concerning the range of conditions under which it takes place and the molecular ratios of the reactants and products. The present paper deals with attempts to gain such information, to discover aspects suitable for further investigation, and to find which of the available procedures is most useful for future preparative applications.

Carboxylation reactions so far investigated fall into two classes. In the first ("type I"; *e.g.*, with phenylacetylene) a vigorous exothermic reaction, during which the nickel carbonyl is apparently consumed as fast as it is added, occurs after a period of quiescence; none of the

acetylenic compound can be recovered. In the second (" type II "; *e.g.*, with 1-ethynyl*cyclo*hexyl acetate) no obvious reaction occurs, but after the reagents have been kept together at 70—80° for 20 minutes a small yield of the expected product is obtained; much of the starting material is recoverable. The latter class, and the catalysed reactions discussed in the preceding paper, were excluded from the present investigations.

The results of applying the reaction to a wide range of acetylenes under approximately uniform conditions have already been described (Part XXII, *loc. cit.*; Part XXIX, *J.*, 1951, 48). The effects of variations in the reaction conditions and the other components employed are discussed below.

(a) *Induction Period and Reaction Temperature.*—The length of the induction period varies with the acetylenic compound used, the solvent and acid employed, and the temperature; it is apparently fairly constant provided that these factors are not varied. The temperature is usually chosen so as to make the induction period conveniently short. For example, for most acetylenic compounds in aqueous-ethanolic acetic acid—" standard conditions " (see Part XXII, *loc. cit.*)—it is about one minute at 70—75°; βγ-acetylenic alcohols, however, require 6—10 minutes even at 80°, while acetylene itself in acetone and concentrated hydrochloric acid reacts readily even at 40°.

(b) *Solvent.*—The nature of the solvent employed appears to be relatively unimportant. Successful—*i.e.*, " type I "—reactions have been observed with phenylacetylene and acetic acid in methanol, ethanol, *iso*propanol, *tert.*-butanol, *n*-butanol, acetone, dioxan, ethyl acetate, pyridine, and anisole. Longer induction periods were observed with *tert.*-butanol, acetone, and especially anisole than with ethanol, while pyridine has a specific effect in reducing the induction period (see previous paper), though its use did not make it possible to effect the reaction at 20°. When primary alcohols were used as solvents a small proportion of the acid formed was esterified, presumably by catalysis by the acetic acid present. In the few cases where this proportion was unusually large (*e.g.*, 5-bromopent-1-yne, diphenylacetylene) the explanation is likely to be prolonged heating during the removal of nickel carbonyl, or an unusually large rate constant for esterification, rather than direct participation of the alcohol in the carboxylation reaction (see below). From a preparative point of view it is desirable to minimise this esterification, as it is always difficult to separate the pure ester from the neutral by-products of the reaction by distillation. Alkaline hydrolysis of the neutral fraction is also undesirable, as α-methylenic esters do not always give good yields of the corresponding acids, perhaps because of alkali-catalysed addition of water or methanol to the double bond; in any case the neutral fraction always contains saponifiable matter other than the expected ester, the non-crystalline acids from which impede the isolation of the main product. Accordingly, the standard conditions, *i.e.*, the use of aqueous-ethanolic acetic acid, are usually to be preferred, even when the ester is required and the use of mineral acids is not excluded, as in the synthesis of simple α-alkyl- or α-aryl-acrylic esters.

(c) *Water.*—The rôle played by water has already been stressed; briefly, the facts observed in the case of typical acetylenic compounds are: (i) with alcoholic solvents the free α-methylenic acid is practically the sole product when acetic acid is used, but esters are obtained in steadily increasing amount as the strength of the acid (" HX ") is increased (see Table I below); (ii) whereas use of aqueous solvents commonly gives yields of 40—50%, very often 45—50%, use of anhydrous solvents with the same acetylenic compounds gives the same products in only 20—30% yields.

The conclusion drawn is that water can participate as the " HY " component in the reaction, but that alcohols cannot. In the absence of added water, side-reactions responsible for the consumption of 70—80% of the acetylenic starting material apparently lead to the formation of enough water to make possible the formation of a certain amount of the α-methylenic acid from the remainder.

(d) *Acid* (" HX ") *Component.*—From the fact that both hydrochloric and acetic acids will participate in the reaction, it was at first believed that their function was merely to maintain a low pH value, and that any acid would suffice. On attempting to verify this hypothesis, however, it was found that effectiveness in the reaction is by no means merely a matter of dissociation constant. The acids which have been tested (by using aqueous ethanol as solvent and typical " reactive " acetylenes) and the results obtained are given in Table I.

The failure of quinol to react is of course not unexpected, in view of its dissociation constant, but that of the other three organic acids is surprising. The most likely explanation for this specificity is that the acid molecules, rather than hydrogen ions, participate in the main reaction.

TABLE I.

Acid.	p*K*.	Acetylene.	Exothermic reaction.	Yield of acid, %.	Yield of ester, %.
Quinol	10	Ph·C≡CH	—	0	0
$Me_2C·CO_2H$	5	do.	+	22 *	0
AcOH	4·7	do.	+	45	2
,, + 1 mol. of NaOAc	—	do.	+	50	0
CH_2:CPh·CO_2H	3·8	do.	—	(92% rec.)	13
,,	—	Bu·C≡CH	—	8	15
H·CO_2H	3·7	Ph·C≡CH	+	23	18
$CH_2Cl·CO_2H$	2·8	Bu·C≡CH	+	18	23
$(CO_2H)_2$	1·4	do.	—	0	0
$CCl_2·CO_2H$	<0	do.	—	0	0
,,		Ph·C≡CH	—	0	0
HCl		do.	+	5	48
H_2SO_4		do.	+	Products not isolated	
H_3PO_4		do.	+	,,	,,

* The isolation of the atropic acid formed was less complete than in other experiments (see Experimental section).

The effects of variations in the reaction components and conditions having been examined, attempts were then made to determine the true quantitative expression of the overall reaction. Here there is the difficulty that the neutral component of the reaction product has in every case proved to be a very complex mixture, from which only one known constituent (apart from the ester of the principal product) has yet been isolated; *s*-triphenylbenzene was obtained when phenylacetylene was used. The investigation was therefore limited to the determination of the ratios involving the acetylenic compound, the nickel carbonyl, and the acid component " HX " (*i.e.*, acetic acid) consumed, and the α-methylenic acid and the bivalent nickel formed. Three problems had to be solved before quantitative work was possible.

(a) *Analytical methods.* It was necessary to determine as accurately as possible the yield of α-methylenic acid formed in the reaction. Attempts to do so by alkali titration proved unsuccessful. Phenylacetylene, or, in one case, but-2-yne-1 : 4-diol diacetate, were therefore used, because the derived acids are non-volatile, readily extracted from water by ether, and easy to crystallise. By using standardised recrystallisation technique and systematically working up mother-liquors it was possible to ensure that practically all the acid formed was isolated as the pure compound, only a trace of semi-crystalline material, perhaps 1% of the total acid fraction, remaining when the final mother-liquors were evaporated.

The standard method employing dimethylglyoxime and ammonium citrate proved satisfactory for measuring the amount of bivalent nickel formed in the reaction. It was hoped that it would also be possible to work with known quantities of nickel carbonyl, and to estimate the amount which had reacted by difference; partly for this reason, and also to make it possible to test the apparatus employed, a method of oxidising the carbonyl in ethereal-alcoholic solution to the ionic state to permit its gravimetric determination was sought. Bromine water proved to be a satisfactory reagent, after dilution of the solution with carbon tetrachloride to increase its density.

(b) *Apparatus.* It was essential to use a method of effecting the reaction such that no serious loss of nickel carbonyl occurred; otherwise the danger of an accidental deficiency of the reagent would necessitate the use of a large excess of carbonyl, and errors introduced by its thermal decomposition would become significant. The apparatus devised has been illustrated (Part XXIX, *loc. cit.*); control experiments described in the Experimental section showed that, though an improvement on the apparatus previously (Part XXII, *loc. cit.*) used, it was not sufficiently reliable to permit the estimation by difference of nickel carbonyl which had reacted (This was not serious, since there is no reason to expect that this quantity would differ from the amount of divalent nickel formed, which could easily be determined.) It was, however, otherwise satisfactory.

(c) *Stability of the nickel carbonyl.* The effects of heating known quantities of nickel carbonyl in various solvents were then examined. Decomposition in aqueous-ethanolic acetic acid at *ca.* 70° is not rapid; a pale green colour slowly developed. In neutral solvents rather more decomposition occurred, probably to nickel oxide, since a black precipitate, which gave a clear solution on addition of mineral acid, was formed.

By making reasonable estimates for the amount of nickel carbonyl added in excess of that required for the reaction, the time, and the temperature, it was concluded that in the quantitative experiments described below the amount of nickel carbonyl thermally decomposed was probably

about 1% of that consumed in the carboxylation reaction. The errors in the estimation of nickel were also of this order of magnitude. No attempt has been made to assess carefully the accuracy of the ratios discussed below, but systematic errors are probably not greater than ±5%, and the precision was more than adequate for the purpose envisaged.

TABLE II.

Reactions with phenylacetylene (50 millimols.)

Expt. no.	Solvent.	AcOH (millimols.) used.	Ni^{++} (millimols.) found.	CH_2:CPh·CO_2H obtained.*	$\frac{CH_2:CPh\cdot CO_2H}{Ni^{++}}$	Remarks.
1	EtOH	33	9·33	21·8(+ 1·0)	2·45	—
2	EtOH	33	8·78	20·2(+ 1·2)	2·43	—
3	EtOH	33	9·34	21·3(+ 1·3)	2·42	—
4	EtOH + NaOAc	33	9·53	24·5	2·57	—
5	$Pr^{i}OH$	33	9·38	22·6	2·41	—
6	$Bu^{t}OH$	33	9·32	22·9	2·46	—
7	$Bu^{t}OH$	33	6·33	15·5	2·45	(*a*)
8	EtOAc	33	9·92	10·2(+ 8·1)	1·84	—
9	$Bu^{t}OH$	33	10·85	25·4	2·33	(*b*)
10	EtOH	13·2	7·72	14·7	1·90	(*c*)
11	EtOH	3·3	6·08	4·3	0·71	(*c*)
12	$Bu^{t}OH$	13·5	7·02	7·8	1·11	(*c*)

(*a*) 6·39 millimols. of $Ni(CO)_4$ used. (*b*) But-2-yne-1 : 4-diol diacetate (50 millimols.) used. (*c*) Note deficiency of acetic acid.

* The weight of atropic acid obtained by hydrolysis of the neutral fraction, shown in parentheses, was included in calculating the ratio.

Results.—A number of experiments on the carboxylation of phenylacetylene were carried out under the standard conditions; the values for the atropic acid and the bivalent nickel formed are given in Table II. The ratio of the yields of these products was reasonably constant, and very near to 2·5, provided that sufficient acetic acid was present. Use of *iso*propanol or *tert.*-butanol in place of ethanol had no effect on the ratio but the use of ethyl acetate (Expt. 8) caused extensive ester-interchange, and a low value for the ratio because of the unsatisfactory yields in the hydrolysis of the ester (see above). Particularly noteworthy is Expt. 7, in which a deficiency of nickel carbonyl was used; it was quantitatively converted into bivalent nickel, and the ratio of the products was exactly the same as in experiments in which the carbonyl was present in excess. It is also interesting to note that when a deficiency of acetic acid was used, the atropic acid formed was quite unable to replace it (contrast Expts. 1—3, and 10); the fact that the ratio then fell below 2·5 indicates that when the acetic acid had been wholly consumed in the carboxylation reaction, phenylacetylene and nickel carbonyl were able to interact with the formation of bivalent nickel but not of atropic acid. This point is further discussed below.

The ratio (α-methylenic acid formed)/(acetylene used) has, in previous discussions from a preparative standpoint, been regarded as the yield of the reaction. In the first six quantitative experiments quoted, this was 46, 42, 45, 49, 45, and 46% respectively; in a larger-scale experiment on phenylacetylene (Part XXII, *loc. cit.*) a yield of 48% is quoted; two experiments in the presence of pyridine (previous paper) gave 49% and 44% yields of atropic acid. Ethynylphenylcarbinyl and ethynylpropylcarbinyl acetates gave yields of 50% and 48% respectively (Part XXII); but-2-yne-1 : 4-diol diacetate gave yields of 53% (Part XXIX) and 51% (above); and tolan (Part XXIX) gave a combined yield (crystalline acid and ester) of 48%. These figures cover every experiment so far carried out in which approximately quantitative isolation of a pure crystalline product was possible and was attempted. While it is conceded that the isolation of such products, even in favourable circumstances, can never be an accurate method of quantitative measurement, it is considered that the above figures and the results in Table II imply that in the Reppe carboxylation reaction, two molecules of the acetylene give rise to one of the product.

Some idea of the quantity of acetic acid needed for the reaction can be obtained from experiments 9, 10, and 11. Those in ethanolic solution, Nos. 9 and 10, show that more (but not much more) than one molecule of atropic acid can be obtained from one of acetic acid.

These results can be summarised in the partial equation:

$$10R\cdot C{\equiv}C\cdot R' + 2Ni(CO)_4 + 5H_2O + 4HX = 5R\cdot C(CO_2H){:}CHR' + 2NiX_2 + (5R\cdot C{\equiv}C\cdot R', 3CO, 4H)$$

The last term must represent the net composition of the very complex mixture of by-products. This expression no doubt describes merely the resultant of a series of inter-related processes, but

it remains essentially correct over a wide range of circumstances, provided that water and the acid used are not deficient (if either is lacking, alternative reactions evidently occur). The molecular ratio (acetylene) : (nickel carbonyl) : (α-methylenic acid) remains quite close to 10 : 2 : 5, and very far from 4 : 1 : 4, for many different acetylenes, acids, and solvents and over a wide range of relative initial concentrations. It is even evident that the acid used (in the case studied, acetic acid) can become the limiting factor, and it is then used up, in ethanolic solution at any rate, more or less according to this equation.

Allusion has been made to the formation of bivalent nickel from mixtures of nickel carbonyl and acetylenic compounds not containing an acid This reaction is easily realised; when nickel carbonyl was added to phenylacetylene in alcoholic solution at 65—70° a mildly exothermic reaction was observed and considerable quantities of dark polymeric material were obtained, from which no pure component (other than about 4% of *s*-triphenylbenzene) could be isolated by chromatography. Essentially similar results were obtained with hex-1-yne, about 35% of the product being distillable at 1 mm. (b. p. 70—140°). These two product-mixtures closely resembled the corresponding neutral fractions obtained in the normal reaction in the presence of acetic acid, and discussed briefly in Part XXII (*loc. cit.*); little, if any, of the acetylene was unchanged. It might be considered that a polymeric product of the type described is an intermediate in the normal carboxylation reaction. Such is apparently not the case; treatment of hex-1-yne with nickel carbonyl in the absence of acid to give the polymeric material, followed by addition of acetic acid, did not result in an exothermic reaction, and no acidic product was obtained.

The results described in this and the previous paper reveal the unsuspected complexity of the Reppe carboxylation reaction Further work on some of the aspects discussed is now in progress in these laboratories.

Experimental.

In obtaining the results shown in Table I the technique described in Part XXIX was employed; 0·02 g.-mol. of the acetylenic compound was used in the first twelve experiments. The acid fraction was isolated with ether and after being thoroughly washed with water was freed as far as possible from volatile acids; in the second experiment the pivalic acid was readily removed by sublimation at 50°/0·5 mm. The atropic acid was carefully recrystallised from light petroleum; the neutral fraction was hydrolysed with aqueous-methanolic potassium hydroxide at room temperature.

Determination of Nickel Carbonyl.—(*a*) The sample (1·2 g.) was dissolved in carbon tetrachloride (100 c.c.) and treated with bromine water in moderate excess. A steady evolution of carbon monoxide occurred; the completion of the reaction was indicated by a permanent orange-brown colour in the lower layer. The layers were separated, the lower being well washed with water, and the nickel in the upper layer and in the washings was precipitated as dimethylglyoxime complex after addition of ammonium citrate, which decomposed the excess of bromine (Vogel, "Quantitative Inorganic Analysis," Longmans, 1939, p. 499).

(*b*) The nickel carbonyl (*ca.* 1·5 g.) was treated with a solution of chromic acid (*ca.* 1·5 g.) in glacial acetic acid (20 c.c.). Slow decomposition resulted; after 2 hours the solution was diluted with water and the nickel was determined. The results obtained in control experiments are tabulated :

Expt.	Method.	$Ni(CO)_4$ used (g.).	Ni content (g.).	Ni^{++} found (g.).	Error, %.
1	*a*	2·031	0·696	0·674	−3·1
2	*a*	1·501	0·515	0·516	+0·2
3	*a*	1·409	0·484	0·486	+0·5
4	*a*	1·814	0·622	0·629	+1·1
5	*b*	0·730	0·251	0·248	−1·2

The accuracy appeared to be adequate for the rough quantitative measurements contemplated. Unfortunately, an attempt to use the convenient colorimetric method employing the oxidised dimethylglyoxime complex (Vogel, *op. cit.*, p. 213) gave inaccurate results when applied to solutions obtained by oxidising nickel carbonyl.

Method (*a*) was readily applied to the distillates obtained when the unchanged nickel carbonyl was removed from the reaction mixture; carbon tetrachloride was added in sufficient quantity to raise the density of the organic layer to *ca.* 1·1, and the decomposition was carried out as described. It was, however, preferable to distil directly into a flask containing 100 c.c. of carbon tetrachloride and 100 c.c. of bromine water when the apparatus described in Part XXIX (*loc. cit.*) was used.

Apparatus.—The simple original apparatus (Part XXII, *loc. cit.*) was tested by heating a known weight of nickel carbonyl in alcoholic solution for 15—30 minutes at 65°, distilling over the excess of carbonyl by adding ether, and determining the nickel present, as carbonyl, in the distillate and that present in the ionic state (after addition of mineral acid, which gave a clear, pale green solution) in the reaction vessel. In these experiments the total recovery was 82, 70, and 46%, 1·5—3·5% of the carbonyl suffering decomposition. The later apparatus (Part XXIX, *loc. cit.*) was then devised; three experiments with it are tabulated below. About 2·6 g. of the carbonyl (accurately weighed into alcohol, with precautions against loss) were heated for about 30 minutes.

Expt.	Solvent (c.c.). EtOH.	H_2O.	AcOH.	Conc. HCl.	Temp.	Unchanged, %.	Decomp., %.	Total recovery, %.
1	50	—	—	—	65—70°	85·2	10·4	95·6
2	50	2	4	—	74—76	84·5	5·8	90·3
3	50	—	—	6	72—74	83·1	9·1	92·2

In Expt. 1—but not Expts. 2 and 3—a black deposit of finely-divided metal and/or oxide formed; it readily dissolved on adding mineral acid.

These results show that the apparatus is not sufficiently reliable to make possible the determination of unchanged nickel carbonyl, but would permit the use of only moderate excess of nickel carbonyl without any danger that loss through evaporation might result in a deficiency. Expt. 2, using the solvent normally employed in the carboxylation (but with a much longer reaction period, at a higher temperature), shows that thermal decomposition of the carbonyl is not an important factor.

Quantitative Experiments.—Reactions were carried out in which phenylacetylene (5·1 g., 50 millimols.), solvent (5 c.c.), acetic acid (2 c.c., 33 millimols.), and water (2 c.c., 100 millimols.) were heated to 65° and treated with a solution of nickel carbonyl (*ca.* 2 ml., 15 millimols.) in ethanol. This was added at such a rate that the temperature remained at 65—70°, to minimise losses; the end of the reaction was indicated by a sharp fall in the temperature, and addition of nickel carbonyl was stopped at this point (previous experience had shown that further addition did not increase the yield, and clearly it would lead to increased thermal decomposition). The mixture was cooled, ether (20 c.c.) was added, and the whole heated until the boiling point of the distillate reached 50°. This procedure was repeated after addition of a further 20 c.c. of ether. The reaction mixture was cooled and poured into 100 c.c. of 3% sulphuric acid; the solution was extracted with ether (3 × 75 c.c.), with care to avoid mechanical losses, and the aqueous layer was used for the gravimetric determination of nickel. The ethereal extract was washed thoroughly with saturated sodium hydrogen carbonate solution; the washings were acidified, and the acid was re-extracted with ether. The dried extract was evaporated to *ca.* 20 c.c. at atmospheric pressure, the remainder of the solvent being completely removed under reduced pressure below 60° (otherwise slight decomposition occurred). The residual solid was warmed to *ca.* 40° with 25 c.c. of light petroleum (b. p. 60—80°), and the solution cooled to 20°. Filtration gave the main crop of atropic acid, m. p. 105—106°, already practically pure. Concentration of the mother-liquors to 5 c.c. gave a second crop (*ca.* 0·1 g.), m. p. 102—105°, which was added to the first; the residue obtained on complete evaporation was only about 0·05 g. of semi-solid material, which was discarded. The neutral fraction was isolated and hydrolysed directly with dilute ethanolic potassium hydroxide solution; a small amount of acidic material was obtained which was recrystallised from benzene–light petroleum to a melting-point of at least 102°.

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167. *The Analysis of Inorganic Compounds by Paper Chromatography. Part III. A Scheme for the Qualitative Analysis of an Unknown Mixture of Cations.*

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A procedure is described for the qualitative analysis of unknown mixtures of the following cations, on a series of paper chromatograms prepared with butanol–benzoylacetone as the mobile phase: Pb, Ag, Hg, As, Sb, Cr, Mn, Cu, Co, Ni, Bi, Fe, Sn, Sr, Ba, Cd, Zn, Al, Mg, Ca, Na, K.

SOME aspects of the analysis of mixtures of cations by paper chromatography, without any previous chemical separation, have already been discussed (Pollard *et al.*, *J.*, 1951, 470). It was indicated that it was not always possible, and often not necessary, to rely entirely on R_F values for the identification of cations. In this paper we describe a scheme for the use of characteristic reactions, which can be applied even to the identification of cations with similar R_F values and is of general application to any mixture of those cations mentioned below. In some mixtures certain cations may be displaced from their normal positions on the chromatogram, and this effect then assists the analysis.

Briefly, the procedure involves the preparation of a number of similar chromatograms of the mixture to be analysed, using butanol–benzoylacetone (Pollard *et al.*, *loc. cit.*) as the mobile phase for the chromatographic separation. The identification is then carried out on individual chromatograms according to the following groups:

Group A. Pb, Ag, Hg, As, Sb.	Group B. Cr, Mn, Cu, Co, Ni, Bi, Fe.
Group C. Sn, Sr, Ba, Cd, Zn, Al, Mg, Ca.	Group D. Na, K.

It is probable that the same scheme can be used for chromatograms prepared with other solvent mixtures.

Experimental.

Dissolution of the Powder.—Two solutions are prepared by boiling about 0·1-g. portions with (*a*) 2 ml. of 2N-nitric acid, and (*b*) 2 ml. of 2N-hydrochloric acid, respectively. Any dichromate or permanganate anions are converted into cations by adding a few drops of hydrogen peroxide. Each solution, after thorough cooling, is centrifuged to remove any precipitate, and the clear supernatant solutions are used for the analysis. Solution (*b*) will not contain Ag, Pb, Hg^+ cations since these are removed as insoluble chlorides. Any other insoluble salts produced, *e.g.* $BaSO_4$, are brought into solution by a suitable method depending on the substance, and analysed separately.

Preparation of the Chromatograms.—Across a sheet (I) of Whatman No. 1 paper, 40 cm. long and 25 cm. wide, is drawn a line, 8 cm. from one end. At distances about 2 cm. apart, spots of the prepared solutions are placed on the line; the first two from solution (*a*) and the rest from solution (*b*).

Another sheet (II) is prepared in the same way with spots from solution (*b*) only. This sheet is then treated so as to precipitate most of the Mn, Co, and Ni ions present, so that these cations will not move on the chromatogram to any great extent and thus tend to mask the fluorescence of the Zn, Al, Cd, Mg, Ca, Sr, and Ba with the kojic acid–oxine (8-hydroxyquinoline) spray (see later). The treatment consists of two sprayings with sodium hypobromite solution, followed by spraying with 2N-acetic acid. The paper is dried over an electric fire between each spraying.

The two sheets, I and II, after drying, are set up in the same tank for chromatgraphy, and run with butanol–benzoylacetone as the mobile phase until the solvent front is about 5 cm. from the end of the paper. (Details of the arrangement of the tank and the composition of the solvent mixture are given in the previous paper; Pollard *et al.*, *loc. cit.*) The sheets are removed from the tank and dried in a current of warm air. Several chromatograms are thus prepared so that some tests, if necessary, can be done in duplicate.

The two chromatograms corresponding to the spots of solution (*a*) on sheet (I) are cut off. The remainder of the chromatograms are sprayed with 2N-hydrochloric acid to "dampness," and dried at 50—60°. This treatment breaks down any non-ionic complexes present. The sheets I and II are cut into strips containing the individual chromatograms, and each strip is suitably labelled.

Analytical Reagents.—Acidic hydrogen peroxide: equal vols. of 2N-sulphuric acid and 20-vol. hydrogen peroxide.

Alkaline hydrogen peroxide: equal vols. of 2N-sodium hydroxide and 20-vol. hydrogen peroxide.

Ammonium mercuric thiocyanate: 2·7 g. of mercuric chloride and 3 g. of ammonium thiocyanate in 100 ml. of distilled water.

Ammonium sulphide: equal vols. of yellow bench solution and distilled water.

Benzidine: 0·05% (w/v) in 10% acetic acid (v/v).

Copper sulphate: 0·1% (w/v) $CuSO_4.5H_2O$ in distilled water containing 10% (v/v) of 2N-sulphuric acid.

Dimethylglyoxime: 1% in industrial methylated spirit.

Diphenylcarbazide: 1% in industrial methylated spirit.

Fluorescent mixture: 0·1 g. of kojic acid and 0·5 g. of oxine in 100 ml. of 60% alcohol

Gallacetophenone: 1% in 2N-ammonia.

Lead–cobalt nitrate: 5 g. of each salt dissolved together in 100 ml. of water with trace of nitric acid. Dilute hydrochloric acid is then added until a precipitate of lead chloride begins to be formed. The solution is filtered if necessary.

Phosphomolybdic acid: 5% (w/v) in distilled water; kept in a dark bottle.

Potassium chromate: 1 g. in 100 ml. of distilled water.

Potassium nitrite: freshly prepared, saturated solution in 2N-acetic acid.

Potassium thiocyanate–acetone: equal vols. of saturated aqueous potassium thiocyanate and acetone.

Quinalizarin: 0·02% (w/v) in industrial methylated spirit.

Rhodizonic acid: freshly prepared 0·1% (w/v) sodium salt in distilled water.

Rubeanic acid: 0·1% (w/v) in industrial methylated spirit.

Sodium hydrosulphite (dithionite): freshly prepared 5% (w/v) in distilled water.

Sodium hypobromite: 2 vols. of 2N-sodium hydroxide saturated with bromine, plus 1 vol. of 2N-sodium hydroxide.

Sodium hypophosphite: 5% (w/v) in N-hydrochloric acid.

Sodium nitrite: saturated solution in distilled water.

Zinc uranyl acetate: saturated solution in N-acetic acid.

Analysis of the Chromatograms.—Each strip of chromatogram is analysed separately by a series of consecutive sprayings or treatments as detailed below. It is important not to make the paper too wet by excessive spraying at any stage. It is often an advantage to spray both sides, since spots often appear on the back. Each coloured or fluorescent spot is marked as it is found, to assist comparison of the positions of cations on the chromatograms in the final conclusions.

Group A, Ag, Pb, Hg^{2+} [Most of any Hg^+ present is oxidised by nitric acid in the preparation of solution (*a*)]. (i) A chromatogram from solution (*a*), sheet II, is sprayed with potassium chromate, and then held over ammonia (*d* 0·880). A brick red spot which fades to pale yellow when treated with ammonia indicates Ag. A bright yellow spot which becomes orange with ammonia indicates Pb (an orange-brown spot with $R_F \simeq 0·3$—0·4, which blackens with ammonia, indicates Hg^+). A blue spot with ammonia, is probably due to Cu. A brown spot with $R_F \simeq 0·1$—0·2 is probaby Mn or Co as

hydroxides. The yellow spot due to Pb shows better contrast if the surrounding potassium chromate stain is destroyed by treatment with sulphur dioxide.

(ii) The strip is now sprayed with 2N-hydrochloric acid, dried, and sprayed with yellow ammonium sulphide when coloured sulphides, etc., are formed, mainly brownish-black. A yellow spot, $R_F \simeq 0{\cdot}2$ is probably due to Cd. A yellow spot $R_F \simeq 0{\cdot}5$, is probably due to As. An orange spot, $R_F \simeq 0{\cdot}1$, probably due to Sb.

The paper is then sprayed with alkaline hydrogen peroxide, warmed over an electric fire, but not dried, and then treated with sulphur dioxide from a siphon, especially where there are dark patches. A dark spot (HgS) at $R_F \simeq 0{\cdot}5$, remaining after this treatment, confirms Hg. The alkaline hydrogen peroxide oxidises all the black sulphides except Hg and usually NiS (which will be nearer the starting line, *i.e.*, $R_F \simeq 0{\cdot}1$; see later tests). If Mn, Co, or Ni is present, it will be precipitated as oxide which is converted by sulphur dioxide into a colourless or faintly coloured spot. Sb is sometimes left as an orange spot, and Cd as a yellow one.

Sub-group. As and Sb. (iii) Another chromatogram obtained from solution (*b*), sheet I, is sprayed lightly with ammonium sulphide. An orange spot, $R_F \simeq 0{\cdot}1$, is probably due to Sb. A yellow spot, $R_F \simeq 0{\cdot}5$, is probably due to As. The spots are marked to distinguish them from any dark sulphides.

The sulphides are dissolved by spraying with concentrated hydrochloric acid and then dried (N.B.: As_2S_3 is not readily dissolved). The paper is sprayed with sodium hypophosphite and held over an electric fire with a thermometer placed directly underneath the paper, and warmed gradually to about 35°. Arsenic shows as a dark brownish spot of $R_F \simeq 0{\cdot}5$. A similar spot for Hg is produced, having $R_F \simeq 0{\cdot}4$, but this has already been identified if present. The strip is now sprayed with phosphomolydic acid and warmed, whereupon Sb is indicated as a " permanent " blue spot, owing to the reduction of the spraying reagent to the " blue " oxide of molybdenum. Any colour caused by residual sulphide fades quickly (10 minutes).

Alternative. Stannous chloride can be used to produce the arsenic stain instead of hypophosphite but, if this is used, the test for Sb has to be done on another chromatogram strip, since the phosphomolybdic acid will be reduced by the stannous chloride if present but is not affected by the presence of hypophosphite.

Group B, Cr, Mn, Cu, Co, Ni, Bi, Fe. (i) A chromatogram from solution (*b*) (sheet I) is sprayed lightly with sodium hypobromite and dried by warming. An orange spot suggests Fe [also with Pb if this has not been completely precipitated when solution (*b*) was prepared]. A blue spot suggests Cu; a dark brown spot, Mn, Co, Ni; a yellow spot, Cr as CrO_4''.

Sub-group, Cr, Mn, Co, Ni. (ii) The strip is now sprayed with acidic (sulphuric acid) hydrogen peroxide; the dark spots due to Mn, Co, and Ni are then slowly converted into faintly coloured sulphates. A Cr spot will become sky blue and then fade quickly ($CrO_4'' \longrightarrow Cr_2O_7'' \longrightarrow$ perchromic acid). A blue Cu spot becomes brown (hydrated copper peroxide) and can be destroyed by spraying it with concentrated hydrochloric acid to " dampness " and then warming over electric fire to remove all the hydrogen peroxide. A confirmatory test for Cr^{3+} as CrO_4'' is to spray the spot with diphenylcarbazide, which immediately becomes purple.

If CrO_4'' is present here, it will interfere with the benzidine test for Mn, which has about the same R_F value, hence it must first be destroyed by reduction with sulphur dioxide to Cr^{3+}; at the same time any NaOBr left on the paper will also be removed. A small excess of benzidine solution is sprayed on the suspected Mn, held over aqueous ammonia (*d* 0·880), and then resprayed with benzidine: a bright blue spot of $R_F \simeq 0{\cdot}1$ indicates Mn (N.B. If excess of benzidine is not used initially, brown MnO_2 may form on exposure to ammonia. If this happens, treatment with sulphur dioxide is repeated, the paper is dried, and the benzidine test repeated).

(iii) The strip is again dried, sprayed with rubeanic acid, and then exposed to aqueous ammonia (*d* 0·880). All other colours produced are ignored except a grey-green spot for Cu, a warm-rusty brown for Co, or a dark Prussian blue for Ni.

Sub-group, Bi, Fe, Co. (iv) Another chromatogram from solution (*b*) (sheet I) is sprayed with potassium thiocyanate–acetone solution. A bright yellow spot indicates Bi; blood red, Fe; bright blue, Co. All these colours are removed by exposure to aqueous ammonia (*d* 0·880), and the paper is then sprayed with excess of dimethylglyoxime, which precipitates the Ni as the very insoluble, red complex which acts as the confirmatory test for Ni and also prevents any interference with the subsequent test for Cu with rubeanic acid, which is then applied as above [see (iii)].

Group C, Sn, Sr, Ba, Cd, Zn, Al, Mg, Ca. The kojic acid–oxine solution is used to spray (1) two chromatograms from sheet I, solution (*b*), and (2) two chromatograms from sheet II, solution (*b*).

Sub-group, Sn, Sr, Ba. The chromatograms from (1) are examined under ultra-violet light after exposure to aqueous ammonia (*d* 0·880), and the positions of the fluorescent spots marked. If a non-fluorescent cation is present, it may produce a region which overlaps the fluorescent spots, or *vice versa*. The cations which produce fluorescence are indicated in the following table (for full details see Pollard *et al.*, Faraday Society Discussion, 1949, no. 1, p. 183).

Cation.	R_F.	Colour.	Brilliance.	Action with acetic acid.
Sn^{2+} and Sn^{4+}	>0·5	Yellow	++	++
Cd	<0·2	Yellow	++	—
Zn	<0·2	Yellow	++	++; sometimes green
Al	<0·2	Green	+++	+++
Mg	<0·2	Blue-green	+++	—
Ca	<0·2	Green	++	—
Sr and Ba	<0·2	Blue-green	+	—

To confirm the presence of Sn as a yellow fluorescent spot of $R_F > 0{\cdot}5$, the strip is shielded with cardboard above this point, and sprayed with 2N-hydrochloric acid, dried, and then sprayed with phosphomolybdic acid and again warmed. A blue spot due to " blue " molybdic oxide indicates Sn^{2+}. If no blue spot appears it is inferred that the fluorescence is due to Sn^{4+}.

The same chromatogram is then sprayed with rhodizonic acid where other fluorescent spots appeared. The formation of a red spot indicates either Sr or Ba, which can be distinguished by further spraying with a mixture of equal volumes of 2N-hydrochloric and 2N-acetic acid. If the red spot vanishes slowly it is due to Sr but, if the colour becomes a brigher red and permanent, then it is due to Ba (N.B. If a small amount of Pb is present, this will yield a red spot with rhodizonic acid, which becomes violet when sprayed with hydrochloric acid, but in preparing (*b*) it was aimed to remove all the Pb in the original mixture).

Sub-group, Cd, Zn, Al, Mg, Ca. Two chromatograms sprayed with the fluorescent mixture, one from sheet I solution (*b*), and one from sheet II (see above), are examined over aqueous ammonia (*d* 0·880) in ultra-violet light. The position and colour of the fluorescent patches are noted and compared with the above table.

The papers are next sprayed very lightly with glacial acetic acid and again examined under ultra-violet light. Fluorescent spots persisting are due to either Al (green) or Zn (yellow); Cd, Mg, Ca, Sr, and Ba are quenched. A separate, fresh chromatogram from sheet I, solution (*b*), unsprayed with fluorescent mixture, is used to confirm Zn. If Co is absent, the paper is sprayed with copper sulphate and then with ammonium mercuric thiocyanate. The formation of a purple or violet-black spot (sometimes very speckled) after 2—3 minutes confirms Zn. If Co is present, this will interfere and so has to be removed by spraying with potassium nitrite to precipitate the Co as potassium cobaltinitrite. The above test for Zn is applied, followed by sulphur dioxide to reduce any nitrous or nitric acid on the paper. The formation of a purple patch round the yellow potassium cobaltinitrite confirms Zn.

A fresh chromatogram from sheet I, solution (*b*), is sprayed with quinalizarin; a bright violet spot is due to Al or Zn. On subsequent spraying with alkaline hydrogen peroxide, the formation of a bright cornflower-blue spot shows Mg (cf. fluorescent tests).

A yellow fluorescent spot, quenched by acetic acid and giving a yellow sulphide with any of the previous ammonium sulphide sprayings, indicates Cd. This can be distinguished from As by the fact that the arsenic sulphide is darkened (reduction to As) on treatment with fresh sodium dithionite, while CdS is unaffected.

If there is a rather weak fluorescent spot which does not respond to any of the above tests and is not quenched by acetic acid, it is attributed to Ca. This may be confirmed with gallacetophenone, which yields a purple spot (Sr and Ba give similar colours, but these will have already been identified).

Group D, Na, K. A chromatogram from sheet I, solution (*b*), is sprayed with 2N-acetic acid, dried, sprayed with zinc uranyl acetate, and examined under ultra-violet light. A blue fluorescent spot at $R_F \simeq 0{\cdot}1$ indicates Na.

The strip is then sprayed with a lead–cobalt nitrate solution, followed by saturated sodium nitrite. The formation, after a few minutes, of the greyish-black triple nitrite of Pb, Co, and K, at R_F 0·1, indicates K. If SO_4'' is present, a preliminary spray of the suspected K area with a saturated aqueous solution of barium nitrate is recommended to precipitate all SO_4'' as barium sulphate. The paper is then dried and sprayed with the necessary reagents to detect K.

This scheme has been tested by several students on a number of analytical mixtures containing up to eight cations associated with a variety of anions. Once the powder has been brought into solution there seems to be no difficulty about identification. As far as we have investigated them, the effect of one cation on another, or the presence of anions like BO_3''', C_2O_4'', and PO_4''', is mainly to modify the relative movements of the cations. Once the chromatograms have been prepared, the time required for identification is usually less than 3 hours; another interesting point is that the dried chromatogram can be kept in the dark for periods up to 3 months before the identification tests are carried out.

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168. *The Direction of Ring Opening of Some Unsymmetrical Ethylene Oxides and Sulphides.*

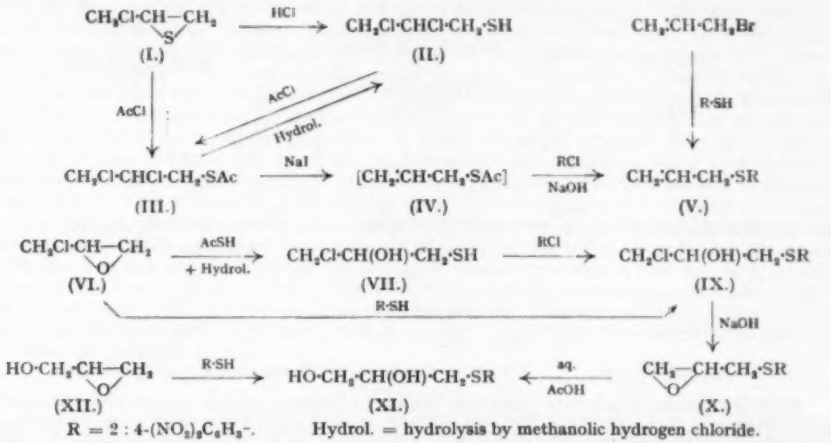
By W. DAVIES and W. E. SAVIGE.

Propylene oxide, *iso*butylene (2-methylpropylene) oxide, epichlorohydrin, and glycidol undergo normal ring fission with 2 : 4-dinitrothiophenol (forming crystalline derivatives suitable for the characterisation of ethylene oxides) and/or thiolacetic acid, the oxygen atom retaining its link with $C_{(2)}$. *iso*-Butylene sulphide with acetic anhydride containing pyridine also gives a " normal " product. Abnormal fissions are brought about by the interaction of chloropropylene sulphide (I) with hydrogen chloride and acetyl chloride respectively. These facts, which have now been proved, admit of a generalisation.

ACETIC ANHYDRIDE in the presence of pyridine has already been shown to react with propylene sulphide to form 2-acetylthiopropyl acetate, $AcS{\cdot}CHMe{\cdot}CH_2{\cdot}OAc$, and this is regarded as a

" normal " process (Davies and Savige, *J.*, 1950, 317) because the sulphur atom retains its link with $C_{(2)}$. Acetyl chloride formed the " abnormal " product, 2-chloropropyl thiolacetate, $CHMeCl{\cdot}CH_2{\cdot}SAc$, aqueous hydrogen chloride also bringing about ring fission in the same direction. The effect of these reagents on other unsymmetrical ethylene sulphides has now been studied.

The unspecified dichloropropanethiol obtained by interaction of chloropropylene sulphide (I) and hydrochloric acid (Culvenor, Davies, and Heath, *J.*, 1949, 285) is shown in the following manner to be the abnormal product—2 : 3-dichloropropane-1-thiol (II). With phenyl



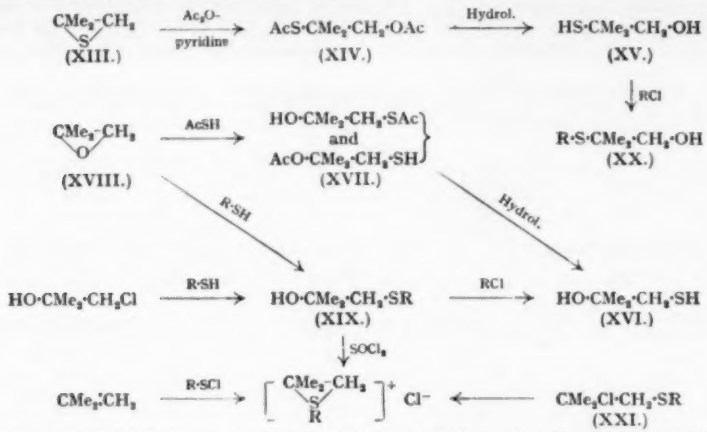
R = 2 : 4-$(NO_2)_2C_6H_3$-. Hydrol. = hydrolysis by methanolic hydrogen chloride.

*iso*cyanate and triphenylmethyl chloride severally, it gives crystalline derivatives identical with those formed from the dichloropropanethiol produced by hydrolysis of the product (III) obtained from (I) and acetyl chloride. Moreover, (III) [which is also made by acetylation of (II)] is dehalogenated by sodium iodide in the manner characteristics of 1 : 2-dihalides. The resulting unstable allyl thiolacetate (IV) is converted into allyl 2 : 4-dinitrophenyl sulphide (V), identical with the product obtained from allyl bromide and 2 : 4-dinitrothiophenol. Hence the abnormal ring fission of chloropropylene sulphide with both hydrogen chloride and acetyl chloride is definitely established.

On the other hand, epichlorohydrin (VI) undergoes normal fission with thiolacetic acid, for the product on acid hydrolysis (Sjöberg, *Ber.*, 1941, **74**, 64) yields 3-chloro-2-hydroxypropane-1-thiol (VII). This gives no ethylene sulphide derivative with mild alkali (cf. Coltof, U.S.P. 2,183,860/1938), and therefore cannot be the isomeric 3-chloro-2-mercaptopropan-1-ol, $CH_2Cl{\cdot}CH(SH){\cdot}CH_2{\cdot}OH$ (VIII). Moreover, (VII) forms a 2 : 4-dinitrophenyl sulphide (IX) which is also obtained by interaction of epichlorohydrin and 2 : 4-dinitrothiophenol in a mild alkaline environment. The chlorohydrin (IX) is readily convertible by cold alkali into the corresponding ethylene oxide (X); on the other hand, it is to be expected that cyclisation of the dinitrophenyl sulphide from the isomer (VIII) would be relatively difficult, and the product would be a trimethylene oxide derivative. The oxide (X) is readily hydrolysed in dilute acetic acid to the glycol (XI), also obtained by interaction of glycidol (XII) and 2 : 4-dinitrothiophenol.

*iso*Butylene (2-methylpropylene) sulphide (XIII) is converted by acetic anhydride containing pyridine into 2-acetylthio-2-methylpropyl acetate (XIV), which is hydrolysed to 2-mercapto-2-methylpropanol (XV). On the other hand, the isomeric 2-hydroxy-2-methylpropane-1-thiol (XVI) is formed on hydrolysis of the mixture (XVII) (owing to " acetyl wandering "; cf. Sjöberg, *Ber.*, 1942, **75**, 27) of 1-acetylthio-2-methylpropan-2-ol and 2-acetoxy-2-methylpropane-1-thiol, produced by interaction of thiolacetic acid and *iso*butylene oxide (XVIII). The mercaptobutanol (XV), but not (XVI), with nascent nitrous acid gives the green and then red colours characteristic of the formation of thionitrites. These colours can be obtained from tertiary, but not from primary or secondary, thiols (Rheinboldt, *Ber.*, 1927, **60**, 184; 1926, **59**, 1311). The isomers (XV) and (XVI) also form different crystalline 2 : 4-dinitrophenyl sulphides. Moreover, the sulphide (XIX) derived from (XVI) is also obtained by interaction of

2 : 4-dinitrothiophenol and either *iso*butylene α-chlorohydrin or *iso*butylene oxide in an alkaline environment. Also, thionyl chloride converts (XIX) without re-arrangement (cf. Fuson, Price, and Burness, *J. Org. Chem.*, 1946, **11**, 477) into the corresponding chloro-sulphide (XXI), previously prepared by Kharasch and Buess (*J. Amer. Chem. Soc.*, 1949, **71**, 2724) from 2 : 4-dinitrobenzenesulphenyl chloride and *iso*butylene.

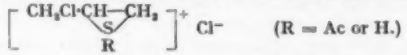


R = 2 : 4-$(NO_2)_2C_6H_3$. Hydrol. = hydrolysis by 1% methanolic hydrogen chloride.

Propylene oxide, which was previously shown to undergo normal fission with thiolacetic acid (Sjöberg, *loc. cit.*; Davies and Savige, *loc. cit.*) is now found to give the " normal " product, 1-(2 : 4-dinitrophenylthio)propan-2-ol when condensed with 2 : 4-dinitrothiophenol. This product is converted by phosphorus pentachloride into the corresponding chloro-sulphide. The readily crystallisable sulphides derived from 2 : 4-dinitrothiophenol are now found to be eminently suitable for characterisation of ethylene oxides, for they are prepared at room temperatures in a weakly alkaline medium. 2 : 4-Dinitrophenyl sulphides have been used to characterise alkyl halides (Willgerodt, *Ber.*, 1885, **18**, 325) and have also been recommended for the characterisation of thiols (Bost, Turner, and Norton, *J. Amer. Chem. Soc.*, 1932, **54**, 1985) and olefins (Kharasch and Buess, *loc. cit.*). In the present work, no difficultly separable mixture of the two possible isomers has yet been obtained from unsymmetrical ethylene oxides, as has been encountered in their reaction with alkali nitrophenoxides (Boyd and Marle, *J.*, 1914, **105**, 2117) or in the reaction of 2 : 4-dinitrobenzenesulphenyl chloride with propylene (Kharasch and Buess, *loc. cit.*).

The normal cleavage of propylene and *iso*butylene oxides, epichlorohydrin, and glycidol occurs almost quantitatively both with 2 : 4-dinitrothiophenol in cold aqueous sodium hydrogen carbonate and with thiolacetic acid. (Fission of glycidol with thiolacetic acid—also with hydrogen sulphide in the presence of alkali—was carried out by Sjöberg, *Ber.*, 1941, **74**, 64.) This recalls similar results with *iso*propylidene 5 : 6-anhydroglucose and hydrogen sulphide or thiols (Ohle and Mertens, *Ber.*, 1935, **68**, 2176), and also the interaction of alkali salts of thiols with unsymmetrical ethylene oxides (Gilman and Fullhart, *J. Amer. Chem. Soc.*, 1949, **71**, 1478). These reactions doubtless belong to the large class based on bimolecular nucleophilic displacements on carbon (cf. Elderfield, " Heterocyclic Compounds," Vol. I, p. 27, Wiley, 1950).

The normal ring fission of *iso*butylene sulphide with acetic anhydride containing pyridine is probably a similar reaction, owing to the presence of pyridine acetate. On the other hand, the abnormal products of the reaction of chloropropylene sulphide with hydrochloric acid and acetyl chloride respectively can be ascribed, as in the case of propylene sulphide (Davies and Savige, *loc. cit.*, p. 319), to the intermediary formation of an ethylenesulphonium ion such as :



(R = Ac or H.)

In such cases the nature of the group (*e.g.*, CH_2Cl) attached to the ethylene sulphide ring should

decide the manner of fission of the C–S bonds in the above ion, but further investigation of this aspect is necessary. Although in several cases the amount of abnormal product from ethylene oxides and acidic reagents is over 50% (Elderfield, *loc. cit.*, pp. 37—39), it is in general small in comparison with the amounts of abnormal products from ethylene sulphides. This is regarded as caused by the smaller tendency of oxygen, as compared with sulphur, to form 'onium ions. These generalisations co-ordinate some reactions of simple unsymmetrical sulphides and oxides, and also clarify some statements in the literature.

From the above considerations, it is likely that the condensation product of two molecules of propylene sulphide with one of *n*-butylamine (Reppe and Nicolai, D.R.-P. 631,016/1936; Frdl., **23**, 244) is $NBu^n(CH_2{\cdot}CHMe{\cdot}SH)_2$ and not $NBu^n(CHMe{\cdot}CH_2{\cdot}SH)_2$. The latter formula has also been queried by Snyder, Stewart, and Zeigler (*J. Amer. Chem. Soc.*, 1947, **69**, 2672), who showed that the main products of interaction of equimolecular amounts of *iso*butylene sulphide and strongly basic primary and secondary amines are normal, *e.g.*, $HS{\cdot}CMe_2{\cdot}CH_2{\cdot}NR_2$. Their demonstration that the interaction of *iso*butylene sulphide and thiols in the presence of an acid reagent (boron trifluoride) is chiefly abnormal is in accord with the results of the present paper. On the other hand, their isolation of chiefly abnormal products ($RS{\cdot}CMe_2{\cdot}CH_2{\cdot}SH$) from *iso*butylene sulphide and thiols in the presence of basic catalysts is, at first reading, contrary to the above generalisations. It is, however, noteworthy that they use a mere trace of basic catalyst (sodium ethoxide), and the large proportion of free thiol may function as an acid environment, leading to some abnormal product. Moreover, as equimolecular amounts of *iso*butylene sulphide and thiol yield only about 40% of the mixed normal and abnormal products, it is not certain that the latter (which usually comprises about 60—80% of the mixture) is in fact the chief product. The results of the present work are more definite, for the normal products (XIV) and the abnormal products (II) and (III) are isolated in yields of over 50% (usually over 80%), and any products of the reverse type that may be formed are in quantities too small to be isolated.

Experimental.

Derivatives of Chloropropylene Sulphide.—2 : 3-Dichloropropane-1-thiol (II), b. p. 74—76°/20 mm., n_D^{15} 1·5245, a liquid having a most unpleasant odour, was prepared from 3-chloropropylene sulphide (I), b. p. 57—60°/45 mm. (cf. Culvenor, Davies, and Pausacker, *J.*, 1946, 1050), and concentrated hydrochloric acid as described by Culvenor, Davies, and Heath (*loc. cit.*) who record b. p. 81°/33 mm. Culvenor (private communication) heated (II) with excess of acetyl chloride on the water-bath for 2 hours and on distillation obtained 2 : 3-dichloropropyl thiolacetate (III), b. p. 122°/25 mm., n_D^{20} 1·5155, a liquid with a characteristic ester odour if pure, but rather unpleasant if contaminated with small amounts of free thiol. The ester (III), b. p. 99—103°/11 mm., was also obtained by heating chloropropylene sulphide and acetyl chloride at 50—55° for 5 hours (cf. Culvenor, Davies, and Heath, *loc. cit.*, who give b. p. 115°/18 mm., n_D^{20} 1·5157), this sample on hydrolysis with 2% of hydrogen chloride in methanol for 2 hours giving a good yield of (II), b. p. 74—77°/20 mm., n_D^{18} 1·5235. Both samples of (II) were unchanged in refractive index throughout the distillation, and identical reactions are as follows. Attempts to cause (II) to react with 1-chloro-2 : 4-dinitrobenzene, 1-fluoro-2 : 4-dinitrobenzene, or picryl chloride were unsuccessful, the alkaline medium (sodium hydroxide, sodium hydrogen carbonate, or sodium acetate) converting (II) into 3-chloropropylene sulphide, as discernible by odour (cf. Coltof, U.S.P. 2,183,860). The thiol (II) and phenyl *iso*cyanate in light petroleum at 160° during 3 hours gave a *thiolcarbanilate*, m. p. 100°, prisms from benzene–light petroleum (Found : N, 5·0; S, 12·1. $C_{10}H_{11}ONCl_2S$ requires N, 5·3; S, 12·1%), which when heated with aqueous sodium hydroxide gave the odour of 3-chloropropylene sulphide. The thiol (II) and triphenylmethyl chloride in light petroleum at 100° during 4 hours (cf. von Meyer and Fischer, *J. pr. Chem.*, 1910, [ii], **82**, 524) gave 2 : 3-*dichloropropyl triphenylmethyl sulphide*, m. p. 128°, plate-like prisms from low-boiling light petroleum in which it is moderately soluble (Found : C, 67·95; H, 5·15. $C_{22}H_{20}Cl_2S$ requires C, 68·2; H, 5·15%).

Dehalogenation of 2 : 3-*Dichloropropyl Thiolacetate* (III).—2 : 3-Dichloropropyl thiolacetate (12·5 g.), sodium iodide (15 g.), and magnesium (10 g.) were refluxed in methyl ethyl ketone (25 ml.) for 24 hours, then poured into water and extracted with ether. The extract was washed with water, dried (Na_2SO_4), and distilled. The halogen-free distillate b. p. 40—160°, was collected and submitted to repeated fractionation, but a constant-boiling fraction could not be obtained. The formation of high-boiling residue during each distillation indicated that polymerisation was occurring. The fraction of b. p. 50—100° (mainly methyl ethyl ketone) contained free thiol, as shown by the characteristic odour and positive reaction with aqueous sodium nitroprusside. The fraction of b. p. 100—140° (of which about 3 ml. were obtained) (1 g.), 1-chloro-2 : 4-dinitrobenzene (0·4 g.), sodium hydroxide (0·4 g.), water (0·5 ml.), and alcohol (10 ml.) were warmed on the water-bath for 15 minutes. Cooling gave *allyl* 2 : 4-*dinitrophenyl sulphide* (V), small yellow plates (0·4 g.), m. p. 71° on recrystallisation from 90% alcohol (Found : N, 11·6; S, 13·5, 13·2. $C_9H_8O_4N_2S$ requires N, 11·65; S, 13·35%). The sulphide (V) was also obtained (m. p. and mixed m. p. 71°) on warming of allyl bromide (0·12 g.) with a filtered solution of 2 : 4-dinitrothiophenol (0·2 g.) and sodium hydroxide (0·4 g.) in alcohol (10 ml.) on the water-bath for 15 minutes, the mixture being then concentrated to 3 ml. and filtered hot and water (0·5 ml.) added (cf. Willgerodt, *loc. cit.*). The product was purified by recrystallisation from aqueous alcohol, then from light petroleum containing a few drops of benzene, and finally dissolved in a mixture of benzene (1 part) and light

petroleum (3 parts), and the solution passed through a small column of alumina and developed with the same solvent.

1-(2 : 4-*Dinitrophenylthio*)-3-*chloropropan*-2-*ol* (IX), m. p. 81—82°, yellow prisms from benzene–light petroleum (Found : C, 37·35; H, 2·75; S, 11·2; N, 9·7. $C_9H_9O_5N_2ClS$ requires C, 36·95; H, 3·05; S, 10·95; N, 9·6%), was obtained from exactly equimolar amounts of 1-chloro-3-mercaptopropan-2-ol (VII) (prepared according to Sjöberg's method, *loc. cit.*), 1-chloro-2 : 4-dinitrobenzene, and sodium hydroxide in alcohol (cf. Bennett and Whincop, *J.*, 1921, **119**, 1863). As shown by a mixed m. p., (IX) was also obtained on mixing epichlorohydrin (0·1 g.) in alcohol with a filtered solution of 2 : 4-dinitrothiophenol (0·2 g.) in saturated aqueous sodium hydrogen carbonate and keeping the mixture for 10 minutes.

2 : 3-*Epoxypropyl* 2 : 4-*dinitrophenyl sulphide* (X), m. p. 94—95°, yellow, halogen-free prisms from benzene–light petroleum (Found : N, 11·0; S, 12·65. $C_9H_8O_5N_2S$ requires N, 10·95; S, 12·5%) was obtained when (IX) in ether–benzene was stirred for 1 hour with excess of cold 40% aqueous sodium hydroxide, and the mixture then poured into water, the organic layer being separated, washed, dried, and freed from solvent. Warming the sulphide (X) with aqueous sodium thiosulphate rapidly produced alkali, which is characteristic of ethylene oxides (cf. Culvenor, Davies, and Heath, *J.*, 1949, 278).

1-(2 : 4-*Dinitrophenylthio*)*propane*-2 : 3-*diol* (XI), m. p. 142—143°, yellow warts from benzene–acetone (Found : S, 11·5. $C_9H_{10}O_6N_2S$ requires S, 11·7%), was obtained in >60% yield when (X) was refluxed in aqueous acetic acid for 4 hours. The diol, which is readily soluble in alcohol and in acetone, but insoluble in benzene, was also obtained when a slight excess of glycidol was mixed with a filtered solution of 2 : 4-dinitrothiophenol (0·2 g.), sodium carbonate (0·2 g.), and sodium hydrogen carbonate (0·2 g.) in water (10 ml.) and the mixture kept for 30 minutes. The solid product was dried at 100°. Its solution in acetone (2 parts) and benzene (1 part) was poured through a narrow column of alumina (10 cm. in length), and the chromatogram developed with acetone. The first yellow fraction yielded (XI) (0·2 g.), identical with the above (mixed m. p.). There appeared to be a small amount of a secondary product contained in a small band near the top of the column, but this gave no crystalline material.

Reaction of iso*Butylene Sulphide with Acetic Anhydride.*—*iso*Butylene sulphide (XIII) was prepared (cf. Culvenor, Davies, and Pausacker, *loc. cit.*) by adding *iso*butylene oxide (23·2 g.) to a well-stirred solution of thiourea (27 g.) in methanol (100 ml.) at a rate such that the temperature was kept at 35—40°. The mixture was then stirred at 40° for an additional 3 hours, diluted with water (200 ml.), extracted with ether, dried, distilled, and refractionated. The yield was 16·5 g. (63%), and the b. p. 84—86°, and 5 ml. of unchanged *iso*butylene oxide were recovered.

*iso*Butylene sulphide (7·1 g.), acetic anhydride (9 g.), and pyridine (0·6 ml.) were heated on the water-bath for 1 hour, and then at 130° for a further 15 hours. The product distilled over the range 110—116°/14 mm., further fractionation yielding 2-*acetylthio*-2-*methylpropyl acetate* (XIV), b. p. 114°/15 mm. (9·0 g.) (Found : C, 50·7; H, 7·6. $C_8H_{14}O_3S$ requires C, 50·55; H, 7·4%). The odour resembles that of the propyl homologue (cf. Davies and Savige, *loc. cit.*). Hydrolysis with hot 1% methanolic hydrogen chloride (6 hours) gave a fraction (3 g.), b. p. 56—64°/15 mm., which gave a light red colour with nitrous acid. Refractionation gave 2-*mercapto*-2-*methylpropan*-1-*ol* (XV) (2·5 g.), b. p. 70°/30 mm., n_D^{22} 1·469 (Found : C, 45·7; H, 9·3. $C_4H_{10}OS$ requires C, 45·3; H, 9·4%). This is partly miscible with water, has the unpleasant odour characteristic of thiols, gives a mauve colour with sodium nitroprusside, and explodes on contact with sodium peroxide. Nitrous acid (cf. Rheinboldt, *loc. cit.*) gives a green flash which soon changes to a light red colour.

2-(2 : 4-*Dinitrophenylthio*)-2-*methylpropan*-1-*ol* (XX), m. p. 108·5°, thick yellow needles from benzene–light petroleum (Found : N, 10·5. $C_{10}H_{12}O_5N_2S$ requires N, 10·3%), was obtained from (XV), 1-chloro-2 : 4-dinitrobenzene, and sodium hydroxide in alcohol [method as for (IX)]. Initial crystallisation was effected by adding light petroleum to a dry benzene solution of the crude oily product and keeping the mixture at 0°.

Reaction of iso*Butylene Oxide with Thiolacetic Acid* (cf. Sjöberg, *loc. cit.*).—*iso*Butylene oxide (7·2 g.) and thiolacetic acid (7·6 g.) were warmed together on the water-bath for 7 hours. The product, apparently consisting of a mixture (XVII) (9·6 g.) of 2-hydroxy-2-methylpropyl thiolacetate and 2-acetoxy-2-methylpropane-1-thiol, distilled over the range 80—100°/12 mm. The first drops of distillate had n_D^{21} 1·4650, whilst the fraction boiling constantly at *ca.* 100° had n_D^{21} 1·4831. Both fractions gave a mauve colour with aqueous sodium nitroprusside. Hydrolysis of (XVII) with 1% methanolic hydrogen chloride (8 hours, reflux) followed by distillation gave a few drops of halogen-containing thiol, b. p. *ca.* 44°/17 mm., then a fraction of b. p. 72—74°/17 mm. The first few drops of this fraction had n_D^{24} 1·4619 and the last few drops n_D^{24} 1·4600. Both portions gave a deep red colour with nitrous acid and a purple colour with sodium nitroprusside, and were partly miscible with water. Redistillation gave pure 2-*hydroxy*-2-*methylpropane*-1-*thiol* (XVI) (80%), b. p. 73—74°/17 mm. (Found : S, 28·5. $C_4H_{10}OS$ requires S, 28·3%).

1-(2 : 4-*Dinitrophenylthio*)-2-*methylpropan*-2-*ol* (XIX), m. p. 95·5°, yellow warts or prisms from benzene–light petroleum (Found : N, 10·55. $C_{10}H_{12}O_5N_2S$ requires N, 10·3%), was readily obtained from (XVI), 1-chloro-2 : 4-dinitrobenzene, and sodium hydroxide in alcohol [method as for (IX)]. It was also obtained, as shown by mixed m. p., (i) on warming of equimolar amounts of *iso*butylene α-chlorohydrin, 2 : 4-dinitrothiophenol, and sodium hydroxide in alcohol on the water-bath for 0·5 hour, then filtration from disulphide and dilution with water, or (ii) from *iso*butylene oxide, 2 : 4-dinitrothiophenol, and aqueous sodium hydrogen carbonate [method as for (IX), the mixture being kept for 1 hour]. The sulphide (XIX) was converted into 2-chloro-2-methylpropyl 2 : 4-dinitrophenyl sulphide (XXI) (Found : C, 41·45; H, 3·65. Calc. for $C_{10}H_{11}O_4N_2ClS$: C, 41·3; H, 3·75%), when warmed on the water-bath with a two-fold excess of thionyl chloride for 0·5 hour, followed by removal of excess of

thionyl chloride by evaporation both before and after addition of small quantities of benzene. The oily product was purified by percolation in benzene–light petroleum through a small column of alumina. The first yellow band was collected, the solvent removed, and the solid residue finally recrystallised from alcohol–light petroleum, giving fine yellow needles, m. p. 86—87°. Kharasch and Buess (*loc. cit.*) also record this m. p. for 2-chloro-2-methylpropyl 2 : 4-dinitrophenyl sulphide.

Reaction of Propylene Oxide with 2 : 4-*Dinitrothiophenol.*—This reaction in aqueous sodium hydrogen carbonate [method as for (XIX)] gave 1-(2 : 4-dinitrophenylthio)propan-2-ol, m. p. 94°, identified by mixed m. p. with sample prepared by Davies and Savige (*loc. cit.*) from 1-mercaptopropan-2-ol, 1-chloro-2 : 4-dinitrobenzene, and sodium hydroxide in alcohol. This was dissolved in chloroform, and phoshorus pentachloride added in portions until effervescence ceased, then ether was added and the solution washed with water. Evaporation of the ether gave 2-chloropropyl 2 : 4-dinitrophenyl sulphide, m. p. 75—77°, yellow, halogen-containing crystals from aqueous methanol and then from chloroform–light petroleum (Found : S, 11·4. Calc. for $C_9H_9O_4N_2ClS$: S, 11·6%). Kharasch and Buess (*loc. cit.*) record m. p. 75—76° for this compound, and 108·5—109·5° for the other possible isomer, both of which they obtained from propylene and 2 : 4-dinitrobenzene sulphenyl chloride.

The microanalyses were made by Miss E. E. Rutherford and Messrs. R. B. Campbell and N. L. Lottkowitz.

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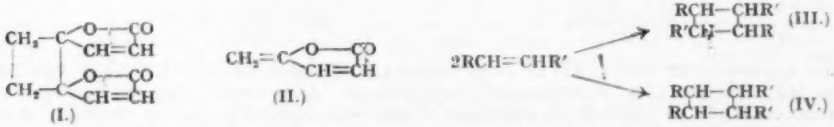
169. *Experiments in the* cyclo*Butane Series. Part I.*

By K. B. ALBERMAN and F. B. KIPPING.

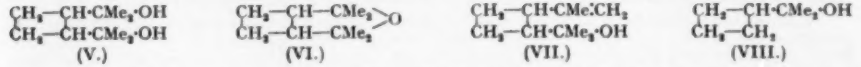
The carbinols are described which result from the action of phenylmagnesium bromide and methylmagnesium iodide on the diethyl esters of *cis*- and *trans-cyclo*butane-1 : 2-dicarboxylic acids. Complete dehydration to a diolefin was achieved in only one case, and experiments on the ozonolysis of this compound are reported.

ANEMONIN has been assigned the structure (I) (Asahina and Fujita, *Acta Phytochim.*, 1922, **1**, 1; *Chem. Zentr.*, 1922, **3**, 712) on the basis of degradation experiments, but no *cyclo*butane derivative has been obtained from it nor has it been synthesised; it is formed by the dimerisation of protoanemonin (II), the structure of which is firmly based on degradation and synthesis (Kipping, *J.*, 1935, 1145; Shaw, *J. Amer. Chem. Soc.*, 1946, **68**, 2510). It seems very probable that a *cyclo*butane ring is indeed produced in the dimerisation and numerous examples of this phenomenon are known. In most recorded cases of the dimerisation of ethylenic compounds, however, the reaction proceeds in such a way that the product is of type (III) rather than of type (IV).



Examples of this are the dimerisation of cinnamic acid to truxillic acid and of ethyl methylenemalonate to tetraethyl *cyclo*butane-1 : 1 : 3 : 3-tetracarboxylate : such a mode of reaction would be expected on general grounds. On the other hand, Lebedeff (*J. Russ. Phys. Chem. Soc.*, 1911, **43**, 820) obtained 1 : 2-di*iso*propylidene*cyclo*butane by the dimerisation of 1 : 1-dimethylallene. By ozonolysis, 2-*iso*propylidene*cyclo*butanone was formed and this on further oxidation gave succinic anhydride. Nevertheless, it seemed of interest to re-examine this diolefin and others of a similar type since they seemed to be possible intermediates for the synthesis of anemonin from a derivative of *cyclo*butane. The preparation of 1 : 1-dimethylallene is, however, unsuited to large-scale operation and the subsequent yield of dimeride is only 5%. The comparatively ready availability of the *cyclo*butane-1 : 2-dicarboxylic acids (Buchman, Reims, Skei, and Schlatter, *J. Amer. Chem. Soc.*, 1942, **64**, 2996) suggested that 1 : 2-di*iso*propylidene*cyclo*butane and other similar compounds could be easily made by the dehydration of the ditertiary alcohols resulting from the reaction of Grignard reagents on the diesters of these acids. *cis-cyclo*Butane-1 : 2-dicarboxylic anhydride was therefore prepared by the above-mentioned method and thence the *trans*-acid by Perkin's method (*J.*, 1894, **65**, 572); the *cis*- and *trans*-diethyl esters were then prepared in the usual way.

Both esters readily gave the respective carbinols (V) with methylmagnesium iodide, but neither could be dehydrated to a diolefin. The *cis*-carbinol gave the tetrahydrofuran (VI), whilst the *trans*-form, from which the formation of a furan would be impossible, also lost only



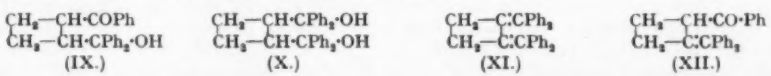
(V.) (VI.) (VII.) (VIII.)

one molecule of water giving probably (VII). The infra-red spectra and the chemical properties support the structures (VI) and (VII), but it is possible that, in the case of the *trans*-isomeride, changes in the ring system have occurred [cf. Chavanne and Chiurdoglu, *Bull. Soc. chim. Belg.*, 1942, **51**, 11, who studied the dehydration of (VIII)].

As the methylcarbinols were therefore unsuited to the object in view, attention was directed to the corresponding phenyl compounds since the dehydration of *cyclo*butyldiphenylcarbinol was known to proceed normally (Kishner, *Chem. Zentr.*, 1911, I, 544): in this case, the *cis*-ester reacted with only three molecules of phenylmagnesium bromide to give (IX) in poor yield, but the *trans*-isomeride reacted in the usual way giving (X) in good yield.

The difference in behaviour between the two esters towards phenylmagnesium bromide, both with regard to the products formed and to the yields obtained, can be ascribed to the considerable steric hindrance associated with the *cis*-configuration. 1 : 2-*trans*-di(hydroxydiphenylmethyl)*cyclo*butane (X) was readily dehydrated by iodine in boiling xylene (Hibbert, *J. Amer. Chem. Soc.*, 1915, **37**, 1748) or, better, by heating it with concentrated hydrochloric acid in glacial acetic acid (Wittig and von Lupin, *Ber.*, 1928, **61**, 1627), and yielded the desired hydrocarbon (XI); and similarly the *cis*-carbinol (IX) gave (XII). The hydrocarbon (XI) formed clusters of fine yellow needles which exhibited an intense green fluorescence under ultra-violet light.

The ultra-violet absorption spectra of these compounds have been examined, and a discussion of the results and their bearing on the configuration and degree of conjugation present in the compounds involved will be communicated elsewhere.



(IX.) (X.) (XI.) (XII.)

Ozonolysis of (XI) yielded different products according to the conditions employed. With a short ozonolysis at −15°, it was possible to isolate the ketone (XIII) in small yield, in addition to benzophenone. With complete ozonolysis at −5°, the only products which could be isolated were benzophenone and succinic acid, as well as a small amount of crystalline material which

(XIII.) (XIV.)

was apparently the tetrol (XIV). These findings agree substantially with those of Lebedeff for the ozonolysis of 1 : 2-di*iso*propylidene*cyclo*butane. As it seemed that *cyclo*butane-1 : 2-dione could not be prepared by ozonolysis or otherwise from such starting materials, other methods for the synthesis of anemonin are being investigated.

Experimental.

(M. p.s are corrected; b. p.s are uncorrected.)

cis-cyclo*Butane*-1 : 2-*dicarboxylic Anhydride*.—A mixture of dimethyl (±)- and *meso*dibromoadipates (2150 g.) gave the anhydride (220 g.; overall yield, 26%) (Buchman, Reims, Skei, and Schlatter, *loc. cit.*).

trans-cyclo*Butane*-1 : 2-*dicarboxylic Acid*.—The *cis*-anhydride (10 g.) and concentrated hydrochloric acid (15 c.c.) were heated at 190° overnight (Perkin, *J.*, 1894, **65**, 572). The crude *trans*-acid was recrystallised from concentrated hydrochloric acid with the addition of charcoal, giving acid (6 g.) of m. p. 130—131°.

Diethyl cis-cyclo*Butane*-1 : 2-*dicarboxylate*.—Dry hydrogen chloride was passed through a solution of the *cis*-anhydride (50 g.) in absolute ethanol (200 c.c.) during 3½ hours, the mixture being allowed to reflux gently. It was then poured into water (500 c.c.). A little carbon tetrachloride was added, the ester layer separated, and the aqueous layer extracted twice with carbon tetrachloride. The combined extracts were washed with sodium carbonate solution and with water and dried ($CaCl_2$). After removal of the solvent, the ester was distilled *in vacuo*, having b. p. 85°/0·5 mm. (47 g., 59%).

Diethyl trans-cyclo*Butane*-1 : 2-*dicarboxylate*.—This was prepared from the *trans*-acid in the usual way: 88 g. of acid yielded 99 g. of ester (91%), b. p. 100°/4 mm. The unused acid from the aqueous

solution and washings was recovered by acidification, evaporation to dryness, and extraction with acetone.

cis-1 : 2-*Di*-(2-*hydroxy*-2-*propyl*)cyclo*butane* (V).—An ethereal solution of *cis*-ester (20 g., 0·1 mole) was added dropwise to a Grignard solution (from methyl iodide, 70 g.; 0·5 mole) during thirty minutes, the heat of the reaction causing the ether to reflux vigorously. After a further hour's refluxing, the mixture was added to crushed ice (500 g.) and ammonium chloride (150 g.). The ethereal layer was separated and the aqueous layer extracted with two 150-c.c. portions of ether. The combined ethereal solutions were washed once with 20% sodium carbonate solution, twice with water, and dried overnight (Na_2SO_4); evaporation of the solvent left a viscous yellow oil which crystallised as clusters of needles (16 g., 93%). The *carbinol* was recrystallised from light petroleum (b. p. 40—60°) from which it was obtained as colourless needles, m. p. 62·5° (Found: C, 69·6; H, 11·75. $C_{10}H_{20}O_2$ requires C, 69·8; H, 11·6%).

(±)-trans-1 : 2-*Di*-(2-*hydroxy*-2-*propyl*)cyclo*butane* was prepared from the *trans*-ester in the same manner (yield, 80%). It crystallised from light petroleum (b. p. 40—60°) as colourless blades, m. p. 94° (Found: C, 69·35; H, 11·5. $C_{10}H_{20}O_2$ requires C, 69·8; H, 11·6%).

Dehydration of the cis-*Carbinol* (V).—The carbinol (3 g.) was refluxed with aqueous oxalic acid (100 c.c.; 6%) during 6 hours. The mixture had now separated into an oily deep-yellow upper layer and a turbid aqueous lower layer. The whole was twice extracted with ether, and the combined extracts were washed successively with sodium carbonate solution and water, then dried ($CaCl_2$), and the ether was removed. The residual yellow oil (3 g.) was distilled under oxygen-free nitrogen and obtained as a colourless mobile liquid with a camphor-like odour, b. p. 57°/20 mm., 67—68°/25 mm. (Found: C, 78·0; H, 11·7. $C_{10}H_{18}O$ requires C, 77·9; H, 11·7%). *Tetrahydro*-2 : 2 : 5 : 5-*tetramethyl*-3 : 4-cyclo*butano*-*furan* (VI) decolourised bromine and permanganate but was not reduced when shaken with hydrogen and palladium at atmospheric pressure.

Dehydration of the trans-*Carbinol* (V).—To the carbinol (17·5 g.), in a 50-c.c. Claisen flask fitted with an 8-cm. Vigreux column and connected to a water-condenser and a cooled receiver, iodine (85 mg.) was added and the temperature slowly raised. Water began to be evolved at 140° and a yellow mobile liquid distilled at 200°. A small amount of dark residue remained, although the distillation had been carried out under nitrogen. The dried distillate [? 1-(2-*hydroxy*-2-*propyl*)-2-iso*propenyl*cyclo*butane*] had b. p. 83—85°/14 mm. and was a colourless liquid with an odour similar to that of the product obtained by the dehydration of the *cis*-isomeride. It decolourised bromine and permanganate (Found: C, 76·6; H, 11·5. $C_{10}H_{18}O$ requires C, 77·9; H, 11·7%). The infra-red absorption spectrum of this compound showed bands at 890 and 1645 cm.$^{-1}$, characteristic of the grouping $>C{=}CH_2$. The dehydration product of the *cis*-carbinol did not show these bands but possessed two absorption bands of equal strength at *ca.* 1375 cm.$^{-1}$, indicative of the presence of two $>CMe_2$ groupings, and not one $\gg CMe$ and one $>CMe_2$.

(±)-2-*Benzoyl*-1-(α-*hydroxydiphenylmethyl*)cyclo*butane* (IX).—A solution of *cis*-ester (5 g., 0·025 mole) in anhydrous ether (20 c.c.) was added dropwise during 30 minutes to a Grignard solution prepared from bromobenzene (19·6 g., 0·125 mole) and magnesium (3·1 g.) in ether (75 c.c.). The yellow solution was refluxed for a further hour and then poured on ice and ammonium chloride as previously described. After removal of the ether, the crude *carbinol* was steam-distilled to remove diphenyl and then recrystallised from alcohol, forming clusters of colourless needles, m. p. 162·5° (1 g., 12%) (Found: C, 84·0; H, 6·4. $C_{24}H_{22}O_2$ requires C, 84·2; H, 6·4%).

(±)-2-*Benzoyl*-1-*diphenylmethylene*cyclo*butane* (XII).—The carbinol (IX) (1 g.) was dissolved in glacial acetic acid (12 c.c.), and concentrated hydrochloric acid (2 c.c.) was added. The mixture was boiled under reflux during 10 minutes, becoming greenish and turbid. The *ketone* was precipitated on cooling as fine colourless needles which, recrystallised from alcohol, had m. p. 94—95° (0·7 g., 78%) (Found: C, 89·05; H, 6·45. $C_{24}H_{20}O$ requires C, 88·9; H, 6·1%). Absorption in ethanol: Max., 2510—2520 and 3220—3250 A.; ε = 25,000 and 400, respectively.

The *oxime* crystallised from alcohol as small colourless prisms m. p. 149° (decomp.) (Found: C, 84·6; H, 6·5; N, 4·5. $C_{24}H_{21}ON$ requires C, 85·0; H, 6·2; N, 4·1%).

(±)-trans-1 : 2-*Di*-(α-*hydroxydiphenylmethyl*)cyclo*butane* (X) was prepared, in the same way as (IX), from the *trans*-ester (10 g., 0·05 mole), bromobenzene (39·25 g., 0·25 mole), and magnesium (6·2 g.). It crystallised from alcohol in stout hexagonal prisms, m. p. 180—181° (19·6 g., 93·5%) (Found: C, 85·9; H, 6·9. $C_{30}H_{28}O_2$ requires C, 85·7; H, 6·7%).

1 : 2-*Bisdiphenylmethylene*cyclo*butane* (XI).—A mixture of the carbinol (X) (15 g.), glacial acetic acid (250 c.c.), and concentrated hydrochloric acid (25 c.c.) was boiled under reflux during 1 hour. The mixture first became yellow, and then yellow needles were precipitated which after recrystallisation from alcohol–benzene (charcoal) gave the *diolefin* as fine pale yellow needles, m. p. 183—184° (9·2 g., 70%) (Found: C, 93·5; H, 6·6. $C_{30}H_{24}$ requires C, 93·75; H, 6·25%). Absorption in ethanol: Max., 2580 and 3510 A.; ε = 23,000 and 21,400, respectively.

Ozonolysis of (XI).—(i) The diolefin (5 g.), dissolved in pure anhydrous chloroform (30 c.c.), was cooled in ice–salt to −15° and ozonized oxygen (3% by wt.) was passed through during 5 hours: the colour, originally orange, had become pale yellow but no solid ozonide separated. The solution was then treated with water (5 c.c.), zinc dust (0·5 g.), and traces of silver nitrate and quinol (cf. Clark, Whitmore, and McGrew, *J. Amer. Chem. Soc.*, 1934, **56**, 177). After removal of the chloroform, the residual oil was separated from the aqueous layer and washed with water which was added to the aqueous layer.

The aqueous layer was neutral to litmus and gave no precipitate on being treated with semicarbazide hydrochloride and sodium acetate.

The non-aqueous layer was again taken up in chloroform, the solution filtered, and the solvent evaporated, giving a red oil which partly crystallised when kept. The crystals gave a green fluorescence under ultra-violet light, indicating the presence of unchanged starting material. The mixture of oil and crystals was then extracted with light petroleum (b. p. 60—80°), and a little of the solution poured on a small alumina column. Five fractions were taken, the column being developed with benzene for the first three and with ethyl acetate for the others.

Fraction	1	2	3	4	5
Volume (c.c.)	20	50	40	50	100
Colour	yellowish green	pale green	colourless	yellow	pale yellow

Fraction (1), after evaporation of the solvent, left a yellow oil which partly crystallised when kept. The crystals, after being pressed on a porous tile, gave the intense green fluorescence characteristic of the starting material. Removal of solvent from fraction (2) left only a trace of material which was combined with the first fraction. The residue from fraction (3) was a minute quantity of a pale yellow oil. This crystallised on being seeded with a small crystal of benzophenone and gave almost colourless needles, m. p. 46—48°. Fraction (4) also consisted of benzophenone, m. p. 43—47°. A sample of benzophenone oxime prepared from fractions (3) and (4) gave a m. p. and mixed m. p. of 144° with an authentic specimen. Fraction (5) left a yellow oil which did not crystallise when seeded with the previous fraction. It was insoluble in water but soluble in alcohol, the yellow solution becoming orange on the addition of alkali.

The remainder of the ozonolysis products originating from the non-aqueous layer were dissolved in chloroform and run on to an alumina column 20 × 30 mm. Most of the material travelled down the column as a deep yellow band which yielded an orange oil after removal of the solvent. This was again taken up in chloroform and run down a small column. The first fraction collected was an orange, partly crystalline syrup. This was washed with alcohol, leaving a fine pale yellow powder, m. p. 132—136° (sintered at 122°). The washings deposited more material which melted at about 100° and possessed the appearance and green fluorescence characteristic of the starting material. The material melting at 132—136° was recrystallised from alcohol, giving 2-*diphenylmethylene*cyclo*butanone* (XIII) as glistening yellow blades, m. p. 140·5° (Found: C, 87·2; H, 6·2. $C_{17}H_{14}O$ requires C, 87·2; H, 6·0%). Absorption in ethanol: Max., 2310 and 3110—3140 A.; ε = 14,600 and 11,200, respectively. The oxime crystallised from alcohol as colourless prisms, m. p. 182—183°.

(ii) The diolefin (5 g.) in anhydrous chloroform (50 c.c.) was ozonised at 0° until titration of the effluent gas showed that an amount of ozone corresponding to two moles had been absorbed: this process required about 10 hours for an initial ozone concentration of about 3%. The originally orange solution had become almost colourless and a crystalline ozonide separated. This was decomposed as previously described and the products separated into aqueous and non-aqueous fractions as before. The aqueous fraction was reddish-brown and was slightly acid. It was extracted with ether which upon evaporation left a pale brown crystalline solid, m. p. 185—186°, mixed m. p. with succinic acid 185—186°. The non-aqueous fraction was a partly crystalline deep-red syrup (4·8 g.) which was washed with alcohol; a colourless residue (0·42 g.) obtained on recrystallisation from chloroform gave 1 : 2-*di*-(*α-hydroxydiphenylmethyl*)cyclo*butane*-1 : 2-*diol* (XIV) as monoclinic prisms, m. p. 192—193° (decomp.) (Found: C, 79·4; H, 5·75. $C_{30}H_{28}O_4$ requires C, 79·7; H, 6·2%).

The remainder of the non-aqueous layer, in alcoholic solution, was poured on an alumina column and eluted with methanol. The first fraction yielded benzophenone (2·8 g., 76% of the theoretical yield allowing for the formation of the tetrol).

Acknowledgment is made to Mr. J. K. Brown for the infra-red examinations, to Dr. R. N. Haszeldine for the determination of the ultra-violet absorption spectra, and to the Colonial Products Research Council for a maintenance grant (to K. B. A.).

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170. *The Preparation and Reactions of* 2 : 4 : 8-*Trinitro*-1-*naphthylamine.*

By E. R. WARD and L. A. DAY.

2 : 4 : 8-Trinitro-1-naphthylamine is obtained by nitration of 8-nitro-1-toluene-*p*-sulphonamidonaphthalene in acetic acid, followed by hydrolysis in sulphuric acid. Its reactions show the effect of steric hindrance from the 2- and the 8-nitro-group. Nitration of 1-bromo- and 1-chloro-8-nitronaphthalenes affords mixtures of halogenotrinitronaphthalenes which have been dehalogenated to the corresponding trinitronaphthalenes. A new route to 7-nitro-1-naphthylamine has been investigated. Improved hydrolyses of mononitrated α- and β-naphthylphthalimide are reported.

2 : 4 : 8-TRINITRO-1-NAPHTHYLAMINE is readily prepared by the dinitration of 8-nitro-1-toluene-*p*-sulphonamidonaphthalene in acetic acid, followed by hydrolysis in sulphuric acid.

Nitration with one equivalent or less of nitric acid still affords the trinitro-compound together with unchanged starting material. The simultaneous dinitration in the 2- and the 4-position is analogous to the dinitrations experienced with the corresponding naphthalides from 1-naphthylamine itself or from 3-, 5-, or 6-nitro-1-naphthylamine (Hodgson and Walker, *J.*, 1934, 180; Hodgson and Turner, *ibid.*, 1942, 723; 1943, 391; Hodgson and Hathway, *J.*, 1944, 561), the nitro-groups entering at the expected 2- and 4-quinonoid positions (Veselý and Jakeš, *Bull. Soc. chim.*, 1923, **33**, 955; Hodgson and Hathway, *J. Soc. Dyers and Col.*, 1945, **61**, 283). The constitution of the trinitronaphthylamine follows from its oxidation to 3-nitrophthalic acid and the ready formation of a diazo-oxide from its diazonium salt showing the adjacence of the nitro- to the amino-group.

The presence of nitro-groups in the 2- and 8-positions, relative to the 1-amino-group, might be expected to lead to a certain amount of steric hindrance in the reactivity of the amino-group, although the reactions of 8-nitro-1-naphthylamine or of 2 : 4-dinitro-1-naphthylamine would not suggest such interference by the 2- or 8-nitro-group alone (cf. Mills and Elliott, *J.*, 1928, 1291; Hunter and Chaplin, *J.*, 1938, 375, 1034). Such diminished activity of the amino-group is now found in attempts to prepare derivatives of the trinitronaphthylamine, in its diazotisation, and in reactions of its diazonium salt. This diminished activity cannot be entirely accounted for by the influence of the 2- and the 4-nitro-group on the basicity of the amino-group [the 8-nitro-group being in a non-quinonoid position will have no effect other than possibly to reinforce the $-I$ effect of the second nucleus (cf. Hodgson and Elliott, *J. Soc. Dyers and Col.*, 1938, **54**, 264)] since it is not shown in the comparable 2 : 4-dinitro-1-naphthylamine which is readily diazotised by Hodgson and Walker's method, and the diazonium salt gives exceptionally good yields in subsequent deamination and Sandmeyer reactions (Hodgson and Walker, *J.*, 1933, 1620; Hodgson and Birtwell, *J.*, 1943, 433).

Thus no reaction could be obtained between 2 : 4 : 8-trinitro-1-naphthylamine and the following reagents: picric acid, 1-chloro-2 : 4-dinitrobenzene, 2 : 3 : 4-trinitrotoluene, 1 : 4-dinitronaphthalene, and *p*-nitrobenzaldehyde. An acetyl compound was obtained with some difficulty. Diazotisation by Hodgson and Turner's method (*J.*, 1943, 86) was only complete after 12 hours, and in subsequent Sandmeyer reactions the yields of 1-bromo- and 1-chloro-2 : 4 : 8-trinitronaphthalenes were very low, their formation being accompanied by large amounts of resinous material containing azo-compounds, the halogeno-compounds being separated from the latter only with great difficulty. Various attempts to prepare 1-iodo-2 : 4 : 8-trinitronaphthalene failed completely. 1-Chloro-2 : 4 : 8-trinitronaphthalene has previously been obtained in an impure form by fractional crystallisation from a mixture with 1-chloro-2 : 4 : 5-trinitronaphthalene, which is the main product of nitration of 1-chloro-2 : 4-dinitronaphthalene (Rindl, *J.*, 1913, 1911; Talen, *Rec. Trav. chim.*, 1928, **47**, 346).

1-Diazo-4 : 8-dinitro-2-naphthol was instantly formed when the diazo-solution prepared as above was poured on ice; it also tends to be formed as a by-product in the Sandmeyer reactions, and its decomposition might account for some of the resinous by-products formed therein. The diazo-naphthol is a comparatively stable compound, and attempts to introduce halogen in place of the diazo-group by Sandmeyer reaction gave largely unchanged material. It could however be deaminated to 4 : 8-dinitro-2-naphthol by being refluxed with a mixture of aluminium and copper powder in ethanol (cf. Hodgson and Turner, *J.*, 1944, 8). Decomposition by copper powder alone was much faster but yields of the deaminated product were lower.

Deamination of 2 : 4 : 8-trinitro-1-naphthylamine should afford 1 : 3 : 5-trinitronaphthalene, a compound previously reported only as a minor product in the nitration of 1 : 5-dinitronaphthalene, and whose existence is not absolutely proven. However, diazotisation of the trinitronaphthylamine and deamination by cuprous oxide alone or with cuprous oxide–methanol afforded as main product 4 : 8-dinitro-2-naphthol. Similar failures to replace the diazonium group by hydrogen have been experienced with 2 : 4 : 6-trinitro-1-naphthylamine (Ward, Ph.D. Thesis, London University, 1948) and with 1 : 4 : 6-trinitro-2-naphthylamine, which afforded only 4 : 6-dinitro-1-naphthol (Hodgson and Hathway, *J.*, 1945, 453).

Against this Hodgson and Hathway (*J.*, 1944, 561) obtained 1 : 2 : 3-trinitronaphthalene by deamination of 2 : 3 : 4-trinitro-1-naphthylamine. Staedel's claims (*Ber.*, 1881, **14**, 898; *Annalen*, 1883, **217**, 153, 173, 174) to have deaminated both 2 : 4 : 5-trinitro-1-naphthylamine and 1 : 6 : 8-trinitro-2-naphthylamine cannot be accepted. He claims to have diazotised 1 : 6 : 8-trinitro-2-naphthylamine in concentrated nitric acid and then decomposed the diazonium salt by pouring it into hot alcohol (*sic*), getting two products (neither in sufficient quantity for analysis), one of which was supposed to be 1 : 3 : 8-trinitronaphthalene. No experimental details of the preparation or deamination of the other trinitronaphthylamine are reported.

Since we desired to examine the properties of an authentic specimen of 1 : 3 : 5-trinitronaphthalene in detail we attempted its preparation by dehalogenation of 1-halogeno-2 : 4 : 8-trinitronaphthalenes using Smith's method (*J. Amer. Chem. Soc.*, 1949, **71**, 2855). It was obvious from the Sandmeyer reactions reported above that we could not obtain the halogeno-compound in any quantity from 2 : 4 : 8-trinitro-1-naphthylamine and we therefore investigated their preparation by dinitration of 1-halogeno-8-nitronaphthalenes (Rindl's method, *loc. cit.*, for preparing 1-chloro-2 : 4 : 8-trinitronaphthalene is unsatisfactory). 1-Chloro- and 1-bromo-8-nitronaphthalenes were readily dinitrated in sulphuric acid but the products were mixtures since on dehalogenation they afforded mixtures of trinitronaphthalenes. On nitrating the dehalogenated product of the dinitration of 1-bromo-8-nitronaphthalene both 1 : 4 : 5 : 8- and 1 : 3 : 5 : 8-tetranitronaphthalene were obtained pure, together with a very small amount of a third product. The production of 1 : 4 : 5 : 8-tetranitronaphthalene demonstrates that the original trinitronaphthalenes must have contained the 1 : 4 : 5-compound (arising from the dehalogenation of 1-bromo-4 : 5 : 8 trinitronaphthalene), and the amount of 1 : 3 : 5 : 8-tetranitronaphthalene produced indicated the presence of a trinitronaphthalene other than the 1 : 4 : 5-isomer. This was therefore probably 1 : 3 : 5-trinitronaphthalene although the 2 : 5 : 8(1 : 4 : 6)-isomer, arising from 1-bromo-2 : 5 : 8-trinitronaphthalene, is not completely excluded. We were unable to separate the mixtures of trinitronaphthalenes nor could we obtain pure 1 : 3 : 5-trinitronaphthalene by treating the mixture in organic solvents with compounds with which it has been reported to form molecular compounds.

We had therefore no alternative but to dehalogenate crude 1-chloro-2 : 4 : 8-trinitronaphthalene (from the Sandmeyer reaction reported above) and from this we obtained a trinitronaphthalene, m. p. 151—152°. This melting point is much higher than that previously reported for 1 : 3 : 5-trinitronaphthalene (Dimroth and Ruck, *Annalen*, 1925, **446**, 123, give 120°). Nevertheless the amount obtained was so small that we are now pursuing alternative routes to its preparation, starting from 1 : 7-dinitronaphthalene.

We have investigated a new route to the rare 7-nitro-1-naphthylamine. Nitration of 1-aceto-4-bromo-8-nitronaphthalide yields a mononitration product which can reasonably be regarded as 1-aceto-4-bromo-2 : 8-dinitronaphthalide. Hydrolysis of this naphthalide followed by deamination to 1-bromo-3 : 5-dinitronaphthalene and subsequent reduction of this by stannous chloride should yield the required product. Unfortunately attempts to hydrolyse the 1-aceto-4-bromo-2 : 8-dinitronaphthalide failed and we have temporarily discontinued the investigation.

An improved procedure for obtaining 8-nitro-1-naphthylamine from the nitration products of α-naphthylphthalimide, by Hodgson and Ratcliffe's method (*J.*, 1949, 1314), is reported and this method has also been applied to the hydrolysis of the similar products from the β-naphthylphthalimide. Hydrolyses of the former mixture with aqueous ethanolic sulphuric acid or with aqueous ethanolic sodium hydroxide failed to give the desired product. Hydrolysis with aqueous ethanolic hydrochloric acid (Hey and Lawton, *J.*, 1940, 281; Hodgson and Dean, *J.*, 1950, 820) gave much lower yields of mixed nitro-amines after long reaction periods.

Experimental.

(Analyses are by Drs. Weiler and Strauss, Oxford.)

α- and β-Naphthylphthalimides were nitrated by Hodgson and Crook's method (*J.*, 1936, 1844).

Improved Preparation of 8-Nitro-1-naphthylamine.—Hydrazine sulphate (450 g.) and sodium hydroxide (280 g.) were dissolved in water (850 c.c.), ethanol (2800 c.c.) was added to the cooled solution, and the precipitated sodium sulphate filtered off. The mixed nitronaphthylphthalimides (560 g.) were then refluxed with this solution for 45 minutes, giving a clear, red liquid, which, after cooling, was acidified with aqueous sulphuric acid (50% w/v) at 0° and filtered, and the residue extracted repeatedly with cold 2N-sulphuric acid (in all *ca.* 5 l.). The combined extracts were basified at 0° with ammonia solution (*d* 0·88). The crude 8-nitro-1-naphthylamine (175 g.; 53%, calculated on the total theoretical yield of nitro-amines) had m. p. 90—95° (cf. Hodgson and Ratcliffe, *J.*, 1949, 1314, who obtained a 36% yield of similar purity).

Improved Hydrolysis of the Mixture of 5- and 8-Nitro-2-naphthylphthalimide.—The mixed nitronaphthylphthalimides (560 g.) were hydrolysed as above for 1 hour, and the residue obtained by pouring the product into water was extracted by boiling hydrochloric acid (10% w/v). The extracts on basification afforded *ca.* 270—300 g. of mixed nitro-amines (80—90%) (cf. Hodgson and Dean, *loc. cit.*, who record a yield of 56%).

8-Nitro-1-naphthylphthalimide.—8-Nitro-1-naphthylamine (2 g.) was fused with phthalic anhydride (2 g.) until frothing ceased (10 minutes). The cooled melt was extracted with boiling acetic acid (50 c.c.) and filtered, and the *phthalimide* obtained by concentration of the extract. Recrystallisation from the same solvent gave needles, m. p. 239·5° (Found: N, 8·6. $C_{18}H_{10}O_4N_2$ requires N, 8·8%).

8-Nitro-1-toluene-p-sulphonamidonaphthalene.—8-Nitro-1-naphthylamine (45 g.) was ground with

toluene-*p*-sulphonyl chloride (135 g.), and pyridine (110 c.c.) added; there was an immediate evolution of heat and considerable frothing. The reaction was completed by heating the solution on the water-bath for 1 hour. The cooled solution was poured into hydrochloric acid (10% w/v; 2 l.) with vigorous stirring. The precipitate was filtered off, washed with dilute hydrochloric acid and then water, and extracted with warm aqueous sodium hydroxide (3% w/v; 1500 c.c.). The extract was filtered and the naphthalide reprecipitated with hydrochloric acid. The yield was almost quantitative (m. p. 152—155°). Recrystallised twice from alcohol the 8-*nitro*-1-*toluene*-p-*sulphonamidonaphthalene* had m. p. 162—166° (Found: S, 9·5. $C_{17}H_{13}O_4N_3S$ requires S, 9·4%). No ditoluene-*p*-sulphonamide was obtained when the reaction was continued for longer periods, a very large excess of toluene-*p*-sulphonyl chloride being used, or when the reaction was carried out in aqueous medium (cf. Hodgson and Ward, *J.*, 1947, 327).

1-*Chloro*-8-*nitronaphthalene.*—8-Nitro-1-naphthylamine (10 g.) was dissolved in boiling glacial acetic acid (50 c.c.), and the solution cooled to 15° and added to sodium nitrite (4·5 g.) dissolved in sulphuric acid (25 c.c.; *d* 1·84) below 30°. After 10 minutes the mixture was poured with vigorous stirring into a solution of cuprous chloride (20 g.) in hydrochloric acid (80 c.c.; *d* 1·2) and left overnight. The product was obtained by pouring the reaction mixture on ice, separated, washed with water, and extracted with boiling ethanol (200 c.c.; charcoal). On concentration to about 50 c.c. the chloro-compound (6·5 g., 60%), m. p. 95—97°, was obtained (Ullmann and Consonno, *Ber.*, 1902, **35**, 2802, give 94—95°). The yield was almost the same when the amine was diazotised in aqueous hydrochloric acid.

1-*Bromo*-8-*nitronaphthalene.*—This was obtained by a similar procedure, cuprous bromide (20 g.) and hydrobromic acid (80 c.c. 48%) being used to decompose the salt. The bromo-compound (6·5 g.; *ca.* 50%) had m. p. 95—98° after recrystallisation from ethanol (Meldola and Streatfeild, *J.*, 1893, **63**, 1057, give 99—100°). A similar yield was obtained by diazotisation in hydrobromic acid.

Nitration of 8-*Nitro*-1-*toluene*-p-*sulphonamidonaphthalene.*—The naphthalide (40 g.) was suspended in glacial acetic acid (80 c.c.) at 65° and a solution of nitric acid (12 c.c.; *d* 1·5) in glacial acetic acid (48 c.c.) added slowly (after the addition of a crystal of sodium nitrite), the temperature being maintained below 80°. The reaction was complete almost immediately and, after cooling in ice, the product was filtered off, and washed with small amounts of glacial acetic acid and then several times with ether. It was dried *in vacuo* (29·7 g., 58%) and on recrystallisation twice from glacial acetic acid the 2 : 4 : 8-*trinitro*-1-*toluene*-p-*sulphonamidonaphthalene* was obtained as cream needles, m. p. 215° (decomp.) (Found: S, 7·2. $C_{17}H_{12}O_8N_4S$ requires S, 7·4%). This compound was hydrolysed by dissolution in twice its weight of sulphuric acid (*d* 1·84), warming it to 40° for 5 minutes, and pouring it on ice. The yield was quantitative. Recrystallised twice from alcohol the 2 : 4 : 8-*trinitro*-1-*naphthylamine* formed orange-yellow needles, m. p. 189—190° (Found: N, 19·8. $C_{10}H_6O_6N_4$ requires N, 20·2%). The trinitro-naphthylamine was recovered unchanged after being refluxed with acetic acid–acetic anhydride–fused sodium acetate for 12 hours. 1-*Aceto*-2 : 4 : 8-*trinitronaphthalide* was however obtained by the following procedure. The amine (0·5 g.) was warmed with acetic anhydride (1 c.c.) and sulphuric acid (1 drop) for 2 minutes, water (3 c.c.) was added dropwise with cooling, and the solution warmed gently and then cooled. The product was recrystallised twice from hot acetic acid, giving creamy plates, m. p. 207° (Found: N, 17·7. $C_{12}H_8O_7N_4$ requires N, 17·5%).

Diazotisation of 2 : 4 : 8-*Trinitro*-1-*naphthylamine.*—The toluene-*p*-sulphonyl derivative (30 g.) was dissolved in sulphuric acid (30 c.c.), hydrolysed by being warmed, and then added to a solution of sodium nitrite (10 g.) in sulphuric acid (50 c.c.) below 20°. The mixture was slowly added, with stirring, to acetic acid (160 c.c.) below 30°. When this solution (12 c.c.) was treated with ice-cold, dry ether (50 c.c.) at 0° and left for a day in the ice-bath it gave a small yield of the solid diazonium sulphate admixed with sodium sulphate (1 g. in all).

1-*Diazo*-4 : 8-*dinitro*-2-*naphthol.*—The above diazonium solution (40 c.c.) (from 5 g. of naphthalide) was poured on crushed ice (200 g.) and the precipitate filtered off, washed with water, and dried *in vacuo* in the absence of light. The 1-*diazo*-4 : 8-*dinitro*-2-*naphthol* (2·7 g.; *ca.* 90%) crystallised from aqueous dioxan (1 : 1) in golden-yellow needles, m. p. 152—155° (decomp.) (Found: N, 21·0. $C_{10}H_4O_6N_4$ requires N, 21·5%).

4 : 8-*Dinitro*-2-*naphthol.*—The diazo-naphthol (2·5 g.) was refluxed with ethanol (75 c.c.), aluminium powder (0·5 g.), and copper powder (0·2 g.) until the liquid no longer coupled with alkaline alcoholic resorcinol (*ca.* 5 hours), charcoal (1 g.) was added and refluxing continued for a further hour. The mixture was filtered, and concentration afforded 4 : 8-*dinitro*-2-*naphthol* (1 g., 45%), which crystallised from sulphuric acid (*d* 1·84) in greenish-yellow needles, m. p. 262—263° (decomp.) (Found: N, 11·8. $C_{10}H_6O_6N_2$ requires N, 11·95%). When copper powder (0·7 g.) was used alone, reaction was complete in 3 hours but the yield was then only 36%; substitution of ethanol by methanol in these reactions produced similar results (cf. Hodgson and Turner, *J.*, 1944, 8). 4 : 8-*Dinitro*-2-*naphthyl acetate* was formed when the dinitronaphthol (0·5 g.) was warmed with glacial acetic acid (1 c.c.) and acetic anhydride (1 c.c.) for 10 minutes. The ester was precipitated by addition of water (5 c.c.) and recrystallised twice from acetic acid, giving plates, m. p. 146° (Found: N, 10·25. $C_{12}H_8O_6N_2$ requires N, 10·2%).

Sandmeyer Reactions with 2 : 4 : 8-*Trinitro*-1-*naphthylamine.*—The toluene-*p*-sulphonyl derivative (3·9 g.; equivalent to 2·5 g. of amine) was diazotised as above and decomposed as follows:

(*a*) With cuprous chloride (8 g.) and hydrochloric acid (40 c.c.; *d* 1·2) at 20° overnight. The mixture was poured on ice, giving a dark brown powder, which was separated, washed with water, and extracted with boiling methanol (100 c.c.; charcoal). The filtered extract on concentration gave crude 1-chloro-2 : 4 : 8-trinitronaphthalene (0·4 g.; m. p. 130—140°), which formed yellow needles, m. p. 152·5—155·5°, from aqueous dioxan (1 : 1) (Rindl, *loc. cit.*, gives 118—126°; Talen, *loc. cit.*, gives 120°) (Found: Cl, 12·4. $C_{10}H_4O_6N_3Cl$ requires Cl, 11·9%). A small amount of dark-red product (m.p. >400°) (probably an azo-compound) was insoluble in the aqueous dioxan (Found: N, 8·7%).

(*b*) With cuprous bromide (12 g.) and hydrobromic acid (50 c.c.; 48%); the procedure was as in (*a*). The ethanol extract afforded dark brown, crude 1-*bromo*-2 : 4 : 8-*trinitronaphthalene* (1·3 g.; m. p. 90—95°) which could not be satisfactorily purified by recrystallisation from organic solvents. Dark brown needles, m. p. 95—115°, were obtained from aqueous dioxan (1 : 1) (Found: Br, 20·15. $C_{10}H_4O_6N_3Br$ requires Br, 23·3%). Again a small amount of dark-red azo(?)-compound (m. p. 326°) was obtained as a by-product.

Attempted Deamination of 2 : 4 : 8-*Trinitro*-1-*naphthylamine.*—Deamination of the diazonium solution described above with cuprous oxide alone or with cuprous oxide–methanol afforded small yields of brown products (m. p. 180—195°), which on crystallisation from warm concentrated sulphuric acid gave pure 4 : 8-dinitro-2-naphthol. The free amine was diazotised similarly and gave the same product. The sulphuric acid residues when poured on ice gave tiny amounts of a golden-yellow substance which had m. p. 117—119° when crystallised from alcohol (Found: N, 14·1%).

Nitration of 1-*Chloro- and* 1-*Bromo*-8-*nitronaphthalenes.*—The halogenonitronaphthalene (15 g.) was suspended in sulphuric acid (100 c.c.; *d* 1·84) and treated at 20° with a mixture of nitric acid (7 c.c.; *d* 1·5) (*ca.* 30% excess for dinitration) and sulphuric acid (28 c.c.; *d* 1·84) for 15 minutes, the temperature being kept below 40°. The mixture was then cooled in ice for 20 minutes, and the precipitate filtered off, washed with water, and dried.

The crude 1-*chloro*-compound (m. p. 180—210°; 11·0 g.) was recrystallised from hot ethanol; the straw-coloured product had m. p. 250—255° [Found: Cl, 12·3. $C_{10}H_4(NO_2)_3Cl$ requires Cl, 11·9%]. The residual liquors from the nitration were poured on ice and yielded a yellow product (0·8 g.), m. p. 60—90°.

The bromonitronaphthalene gave a cream *trinitro*-compound (m. p. 160—162° after shrinking at 152°) (14 g.), which, after crystallisation from hot ethanol, melted sharply at 168—169° (shrinking from 152°) Found: Br, 23·6. $C_{10}H_4O_6N_3Br$ requires Br, 23·3%). The residual filtrate gave a product (4 g.; m. p. 120°) which was more soluble in ethanol than the first.

Dehalogenation of Halogenotrinitronaphthalenes.—The general procedure was that used by Smith (*loc. cit.*) (cf. Rindl, *loc. cit.*) for preparing 1 : 3-dinitronaphthalene from 1-chloro-2 : 4-dinitronaphthalene.

(*a*) The bromotrinitronaphthalene (10 g.) from the nitration of 1-bromo-8-nitronaphthalene, after removal of the copper bronze and excess of benzoic acid, was extracted with ethanol (50 c.c.). On cooling the extract deposited a yellow-orange substance (4 g.) which on recrystallisation from ethanol had m. p. 108—109° (2 g.) (Found: C, 46·4; H, 1·85. Calc. for $C_{10}H_3O_6N_3$: C, 45·6%; H, 1·9%).

This was very soluble in dioxan, ether, benzene, toluene, and chloroform; it was not sublimed by being heated to 180° at 15 mm. It gave the following colour reactions, suggestive of a trinitronaphthalene: cherry red with a cold aqueous ethanol solution of sodium sulphite, red becoming brown with sodium hydroxide in aqueous acetone, and pale red on being heated with aqueous sodium hydroxide. When it (0·2 g.) was dissolved in the minimum quantity of chloroform and a saturated solution of β-naphthol added there was no precipitate, and concentration only afforded mixed crystals of the two reactants, there being no evidence of the formation of a molecular compound (cf. Dimroth and Ruck, *loc. cit.*). No molecular compounds could be obtained with α-naphthylamine, β-naphthylamine or diphenylamine (cf. Sudborough and Karvé, *J. Indian Inst. Sci.*, 1921—1922, **4**, 43). The "trinitronaphthalene" (2 g.) was added to a mixture of nitric acid (8 c.c.; *d* 1·5) and sulphuric acid (10 c.c.; *d* 1·84) with stirring at 20°, and the mixture cautiously warmed to 80—90° until frothing ceased (about 10 minutes), then on a water-bath for 30 minutes. After cooling to 0° the solid which separated was removed, repeatedly washed with water, and then repeatedly extracted with boiling acetone (150 c.c. in all); the residue (0·23 g.) had m. p. 375° (decomp.) and was identical with an authentic specimen of 1 : 4 : 5 : 8-tetranitronaphthalene. The acetone extracts on concentration (to 20 c.c.) deposited a white product (0·07 g.), m. p. 280° (decomp.), consisting mainly of needles with bifurcate ends with smaller amounts of cubic crystals. The residual acetone solution on evaporation to dryness affording almost pure 1 : 3 : 5 : 8-tetranitronaphthalene (0·5 g.), identical with an authentic specimen. 0·23 g. of 1 : 4 : 5 : 8-tetranitronaphthalene would be produced from about 0·8 g. of 1 : 4 : 5-trinitronaphthalene which at the same time would yield only about 0·1 g. of 1 : 3 : 5 : 8-tetranitronaphthalene (Ward and Day, unpublished work).

(*b*) The chlorotrinitronaphthalene (10 g.) from the nitration of 1-chloro-8-nitronaphthalene in a similar manner gave an orange-yellow product (0·6 g.; m. p. 108—125°) with properties similar to those of the substance reported above.

(*c*) Crude 1-chloro-2 : 4 : 8-trinitronaphthalene (5 g.), from the Sandmeyer reaction described above, gave a yellow-orange product (0·4 g.; m. p. 141—146°). Recrystallised from aqueous dioxan (1 : 1) it had m. p. 151—152° (Found: N, 15·5. Calc. for $C_{10}H_3O_6N_3$: N, 16·0%). The mixed melting point with the starting material was 119—130° and with 1 : 4 : 5-trinitronaphthalene was 116—125° (1 : 4 : 5-trinitronaphthalene has m. p. 149°). The Lassaigne test showed the absence of chlorine.

Preparation and Attempted Hydrolysis of 1-*Aceto*-4-*bromo*-2 : 8-*dinitronaphthalide.*—1-Aceto-8-nitronaphthalide was easily prepared by dissolving 8-nitro-1-naphthylamine (5 g.) in warm glacial acetic acid, adding acetic anhydride (5 c.c.), and refluxing for 10 minutes. This was converted directly into its 4-bromo-derivative by adding more glacial acetic acid (10 c.c.) followed by a solution of bromine (1·5 c.c.) in acetic acid (15 c.c.), added dropwise. The solution was refluxed for 1 hour and charcoal added after 45 minutes. The hot solution was filtered and concentrated giving 1-aceto-4-bromo-8-nitronaphthalide which when recrystallised from alcohol had m. p. 197—201° (Hodgson and Crook, *J.*, 1936, 1338, give 202°), depressed by 1-aceto-2 : 4-dibromo-8-nitronaphthalide.

The naphthalide was nitrated by adding it slowly to nitric acid (5 c.c.; *d* 1·5) at 0°, the temperature being kept at 5—10° until it became steady (30 minutes). The mixture was poured into ice-water

(250 g.), and the product separated, washed with water, and dried *in vacuo* (yield 1·7 g., 98%). Recrystallised from aqueous acetic acid (60% v/v) the 1-*aceto*-4-*bromo*-2 : 8-*dinitronaphthalide* formed micro-crystals, m. p. 208—211° (Found : Br, 22·5. $C_{12}H_5O_5N_2Br$ requires Br, 22·6%). When heated under reflux for periods of up to 10 hours with aqueous ethanolic hydrochloric acid or aqueous ethanolic sulphuric acid (60% w/v) the dinitronaphthalide was largely recovered unchanged.

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171. *Attempts to Prepare New Aromatic Systems. Part III.* cyclo*Pent*[a]*indene.*

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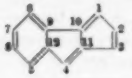
In continuation of experiments designed to synthesise *cyclo*pent[*a*]indene (I) a much improved preparation of the ketone (IV) has been found in the reaction of *cyclo*pent-1-enecarboxyl chloride (II) with benzene in presence of aluminium chloride at the boiling-point. Reduction of (IV) gave the hexahydro*cyclo*pent[*a*]indene (V), but dehydrogenation of this hydrocarbon to *cyclo*pent[*a*]indene (I) has not been successful. Reaction of the 3-keto-2-phenyl*cyclo*pentane-1-carboxylic acid (X) with phosphoric anhydride proceeded abnormally to give 2-phenyl*cyclo*pent-2-enone (XV) by loss of the elements of formic acid. The action of acetic anhydride in the cold on (X) gave the enol acetate (XI) but, on heating, the reaction proceeded further to give the complex acetoxy-lactone (XIII).

EXPERIMENTS having as their object the synthesis of the unknown hydrocarbon *cyclo*pent[*a*]indene (I) were described by Baker and Leeds in Part I of this Series (*J.*, 1948, 974). *cyclo*Pent[*a*]indene * is of interest in that it is the simple benzo-derivative of pentalene, the latter being a possible, but as yet unknown, compound of aromatic type consisting of two fused five-membered rings containing, formally, four double bonds (see Part I).

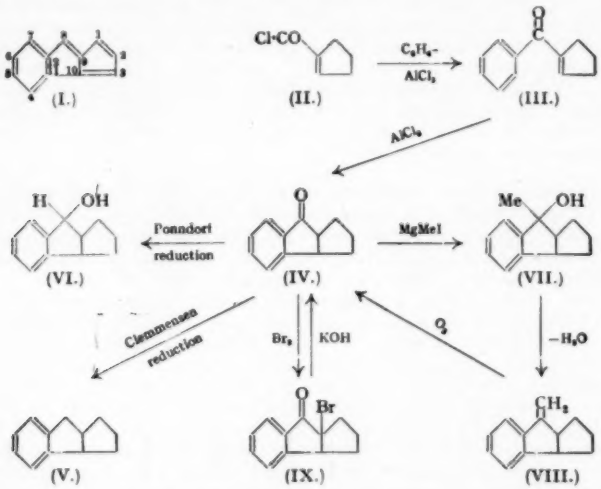
It was shown (*loc. cit.*) that a compound with the desired carbon skeleton, namely 1 : 2 : 3 : 8 : 9 : 10-hexahydro-8-keto*cyclo*pentindene * (IV), could be prepared by condensing benzene with *cyclo*pent-1-enecarboxylic acid and aluminium chloride at the boiling point, isolating the 2-phenyl*cyclo*pentane-1-carboxylic acid, and then cyclising it with a phoshoric anhydride–phosphoric acid mixture to the ketone (IV). This synthesis is, however, not very practicable because the reaction between benzene and *cyclo*pent-1-enecarboxylic acid is complex and gives the desired acid in only about 8% yield; neutral material and much 3-phenyl*cyclo*pentane-1-carboxylic acid are formed owing to migration of the double bond in *cyclo*pent-1-enecarboxylic acid under the influence of the aluminium chloride. Nevertheless this type of reaction appeared to be the most promising for the preparation of the hexahydroketo*cyclo*pent[*a*]indene (IV), and further work was undertaken.

*cyclo*Pent-1-enecarboxyl chloride (II) reacts with benzene at room temperature to give 1-benzoyl*cyclo*pentene (III) by a simple Friedel–Crafts reaction. This ketone is oxidised by potassium permanganate to benzoic acid. The position assigned to the double bond is supported by the bright red colour of the 2 : 4-dinitrophenylhydrazone. The ketone (III) when heated with benzene and aluminium chloride undergoes cycloisomerisation to the desired tricyclic ketone (IV) identical with that previously prepared by Baker and Leeds (*loc. cit.*). In preparing (IV) it is not necessary to isolate the intermediate (III), and it is conveniently made directly from the acid chloride (II) in 58% yield by reaction with benzene and aluminium chloride at the boiling point. Unsuccessful attempts to bring about the addition of benzene to 1-cyano*cyclo*pentene (an intermediate in the preparation of II) in presence of hydrogen chloride

* In *J.*, 1948, 974, this ring-system was numbered  but the Ring Index method (as in I) is now preferred—EDITOR.

and either aluminium chloride or zinc chloride led to the isolation of 1-chloro-2-cyano*cyclo*pentane and 2-chloro*cyclo*pentan-1-carboxyamide respectively. It is interesting to note that in the preparation of the ketone (IV) by the present method, there is no formation of the isomeric ketone, 1 : 3-*endo*ethylene-4-keto-1 : 2 : 3 : 4-tetrahydronaphthalene, which is produced by reaction of benzene with *cyclo*pent-1-enecarboxylic acid along with much of the intermediate 3-phenyl*cyclo*pentane-1-carboxylic acid (see Part I). It appears that in the acid chloride (II) and in the ketone (III) there is no tendency for the double bond to wander as in *cyclo*pent-1-enecarboxylic acid, and this may be ascribed to the degree of conjugation being greater (owing to increased cationoid character of the carbon atom of the carbonyl group) in the acid chloride (II) and the ketone (III) than in the free carboxylic acid.

Reduction of (IV) by the Clemmensen method in presence of toluene gave 1 : 2 : 3 : 8 : 9 : 10-hexahydro*cyclo*pent[*a*]indene (V), and this hydrocarbon was characterised as a monosulphonamido-compound, probably the 6-derivative. Many attempts were made to dehydrogenate (V) to *cyclo*pent[*a*]indene (I), but no conclusive evidence was obtained of the production of any less saturated material with aromatic properties. The methods investigated, which are not described in the Experimental section, included boiling with either palladium–charcoal, platinum–charcoal, or selenium, and passage of the vapour over (*a*) palladium–charcoal and asbestos at 330—350° under reduced pressure (see apparatus described by Nunn and Rapson, *J.*, 1949, 825, 1051) or (*b*) platinum–charcoal at 340° in a stream of nitrogen at atmospheric pressure (see apparatus described by Read and Dewar, *J. Soc. Chem. Ind.*, 1936, **55**, 347τ).

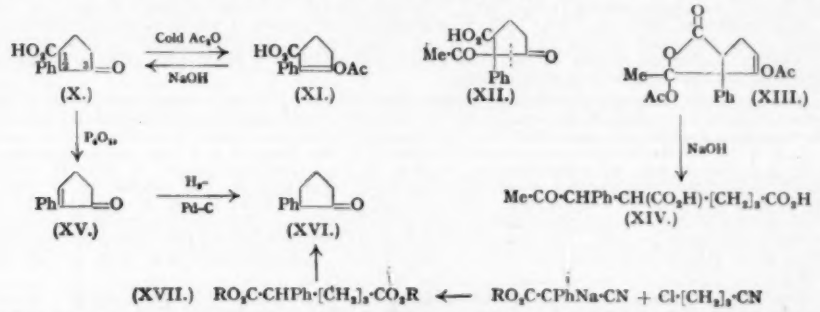


As direct dehydrogenation of (V) had failed, other methods which might lead to *cyclo*pent[*a*]indene were investigated starting from the ketone (IV). Reduction to the secondary alcohol by the Ponndorf method proved difficult and only partial reduction took place giving a mixture of 1 : 2 : 3 : 8 : 9 : 10-hexahydro-8-hydroxy*cyclo*pent[*a*]indene (VI) and much unchanged ketone (IV). The hydroxy-compound was freed from the ketone by several treatments with Girard T reagent, and was finally characterised as the *p*-nitrobenzoyl and the α-naphthylurethane derivatives. Treatment of (IV) with methylmagnesium iodide gave 1 : 2 : 3 : 8 : 9 : 10-hexahydro-8-hydroxy-8-methyl*cyclo*pent[*a*]indene (VII), a solid which underwent dehydration at 120° to the fluid 1 : 2 : 3 : 8 : 9 : 10-hexahydro-8-methylene*cyclo*pent[*a*]indene (VIII). The structure assigned to this product, which may not be homogeneous, is based on the fact that ozonolysis gave the ketone (IV), though in poor yield; the double bond is unlikely to be between carbon atoms 8 and 9 as this mono-olefin would be considerably strained. Bromination of the ketone (IV) in acetic acid gave 9-bromo-1 : 2 : 3 : 8 : 9 : 10-hexahydro*cyclo*pent[*a*]indene (IX), which was virtually stable towards silver oxide, potassium acetate, pyridine at 120°, or quinoline at 170°. With ethanolic potassium hydroxide the bromine atom was replaced by hydrogen and the ketone (IV) was regenerated. This is clearly a case of " positive " halogen in the

α-position to a carbonyl group being replaced by hydrogen; the reaction is much better known in the case of reduction by halogen acids, particularly hydriodic acid, than by alkalis (see Lapworth, *J.*, 1899, **75**, 1134; *Mem. Proc. Manchester Lit. Phil. Soc.*, 1920, **64**, ii, 8; Gilman, "Organic Chemistry," 2nd Edn., 1942, Vol. I, 854).

As the foregoing experiments with the ketone (IV) did not appear promising, attention was turned to the possible use of 3-keto-2-phenyl*cyclo*pentane-1-carboxylic acid (X) as an accessible starting point for the synthesis of *cyclo*pent[*a*]indene (I). This acid (X) is an intermediate in one of the syntheses of the ketone (IV) described in Part I, and it was hoped that it might be cyclised to 1 : 2 : 3 : 8 : 9 : 10-hexahydro-3 : 8-diketo*cyclo*pent[*a*]indene which would be a very promising starting point for the preparation of *cyclo*pent[*a*]indene by purely chemical methods rather than by catalytic dehydrogenation at fairly high temperatures. Cyclisation of the acid (X) has not yet been achieved, although a variety of methods has been tried, but the experiments have revealed some rather remarkable properties of this compound.

When treated with acetic anhydride at room temperature in presence of a little sulphuric acid, (X) was converted into its enol acetate, 3-acetoxy-2-phenyl*cyclo*pent-2-ene-1-carboxylic acid (XI), and this substance regenerated the keto-acid (X) on alkaline hydrolysis The position assigned to the double bond in the enol acetate (XI) is the more probable of the two possibilities as it gives the greater degree of conjugation. The action of hot acetic anhydride on the keto-acid (X), $C_{13}H_{12}O_3$, gave a substance which showed neither acidic nor ketonic properties and whose analysis showed it to be a triacetyl derivative of (X), *i.e.*, $C_{19}H_{18}O_6$. Determination of the acetyl groups by alkaline hydrolysis showed that two only were removed as acetic acid and these must be regarded as *O*-acetyl groups, so that the third must be attached to carbon. We regard the compound, $C_{19}H_{18}O_6$, as the acetoxy-lactone (XIII); it probably arises from the enol acetate (XI) as follows. Migration of the acetyl group from oxygen to carbon atom 2 first occurs, to give the diketone (XII); this then forms the enol acetate at the 3-carbonyl group, and, as a γ-keto-acid, gives the lactone (XIII). An analogy for the migration of the acetyl group in (XI) is afforded by the rearrangement of *O*-acetyl- to *C*-acetyl-acetoacetic ester



(Claisen and Haase, *Ber.*, 1900, **33**, 3778; Wislicenus and Körber, *Ber.*, 1901, **34**, 218; Bouveault and Borgert, *Bull. Soc. chim.*, 1902, **27**, 1160; Wislicenus, *Ber.*, 1905, **38**, 546; Dieckman and Stein, *Ber.*, 1904, **37**, 3373), and there are many cases, *e.g.*, lævulic acid, of γ-keto-acids which yield acetoxy-lactones when treated with acetic anhydride. Support for the structure (XIII) is afforded by the isolation, after complete hydrolysis by boiling with 10% aqueous sodium hydroxide, of a dicarboxylic acid containing a *C*-acetyl group as proved by a positive iodoform reaction. This dicarboxylic acid has clearly arisen by opening of the *cyclo*pentanone ring in the 1 : 3-diketone (XII) (cf. ring opening of acyl*cyclo*hexanones investigated by Hauser, Swamer, and Ringler, *J. Amer. Chem. Soc.*, 1948, **70**, 4023) which is undoubtedly an intermediate in the alkaline hydrolysis of (XIII). This acid must, therefore, be regarded as 5-keto-4-phenylhexane-1 : 3-dicarboxylic acid (XIV).

Cyclodehydration of the ketonic acid (X) was attempted by heating it with a mixture of phosphoric anhydride and syrupy phosphoric acid, a procedure which has proved very satisfactory for the cyclisation of 2- and 3-phenyl*cyclo*pentane-1-carboxylic acids (Part I). Recent investigation has shown that polyphosphoric acid is probably the active agent in these cases (Snyder and Werber, *J. Amer. Chem. Soc.*, 1950, **72**, 2962, 2965). The reaction yielded a solid, neutral ketone, $C_{11}H_{10}O$, which gave benzoic acid on oxidation with alkaline potassium permanganate and had been derived from the keto-acid (X) merely by the loss of the elements

of formic acid. This ketone must be 2-phenyl*cyclo*pent-2-enone (XV); catalytic reduction gave 2-phenyl*cyclo*pentanone (XVI), characterised by a 2 : 4-dinitrophenylhydrazone and an oxime which were identical with those derived from 2-phenyl*cyclo*pentanone synthesised from α-phenyladipic acid (XVII; R = H) by esterification, cyclisation, and final hydrolysis and decarboxylation. The position assigned to the double bond in (XV) is based on the orange-red colour of the derived 2 : 4-dinitrophenylhydrazone and on its almost certain conjugation with both the phenyl and the carbonyl group. α-Phenyladipic acid was previously prepared by Case (*J. Amer. Chem. Soc.*, 1933, **55**, 2929) from the sodio-derivative of ethyl phenylmalonate and γ-iodobutyronitrile; in this work it was prepared from rather more accessible intermediates, namely the sodio-derivative of ethyl α-cyanophenylacetate and γ-chlorobutyronitrile. We find that the preparation of 2-phenyl*cyclo*pentanone from 2-chloro*cyclo*pentanone and phenylmagnesium bromide described by Mitchovitch (*Compt. rend.*, 1935, **200**, 1601) is unsatisfactory, giving a non-homogeneous product in poor yield; the high melting point which he records may be accounted for by the fact that 2-phenyl*cyclo*pentanone is curiously unstable and passes, when kept, into much-higher-melting material (see Experimental).

There is no evidence to suggest the mechanism of the loss of the elements of formic acid from the ketone (X), which may be either direct, or indirect involving a shift of the double bond of the enol form to the 1 : 2-position followed by an allylic rearrangement and loss of the elements of formic acid from the α-hydroxy-acid so produced.

Experimental.

1-*Benzoyl*cyclo*pentene* (III).—*cyclo*Pent-1-enecarboxylic acid (10·5 g.; Cook and Linstead, *J.*, 1934, 958, and modification given by Baker and Leeds, *loc. cit.*) and thionyl chloride (101 c.c.) were heated on the steam-bath for ½ hour and distilled, giving *cyclo*pent-1-enecarboxyl chloride (II), b. p. 65—67°/16 mm. (95 g., 78%) (Kenner and Wain, *Ber.*, 1939, **72**, 459, do not record the method of preparation, but give b. p. 179—180°/758 mm.). The chloride (8·1 g., 1 mol.) in dry benzene (100 c.c.) was cooled in ice, and aluminium chloride (25 g., 3 mols.) added during ½ hour. After 20 hours at room temperature, the mixture was poured on ice and concentrated hydrochloric acid (50 c.c.), and the benzene layer separated, washed with dilute aqueous sodium hydroxide, dried ($MgSO_4$), and distilled, giving 1-*benzoyl*cyclo*pentene* (III) as a colourless oil (5·6 g., 52%), b. p. 143°/12 mm., d_{18}^{18} 1·068 (Found: C, 84·1; H, 7·3. $C_{12}H_{12}O$ requires C, 83·7; H, 7·0%). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol as red plates, m. p. 162—163° (Found: C, 61·9; H, 4·7; N, 15·9. $C_{18}H_{16}O_4N_4$ requires C, 61·4; H, 4·6; N, 15·9%). Oxidation of this ketone (0·56 g.) by boiling it for 5 hours with alkaline potassium permanganate gave benzoic acid (0·16 g., 40%).

1 : 2 : 3 : 8 : 9 : 10-*Hexahydro*-8-*keto*cyclo*pent*[a]*indene* (IV).—(a) *From* 1-*benzoyl*cyclo*pentene*. The ketone (III) (2·17 g., 1 mol.) in dry benzene (50 c.c.) was treated with aluminium chloride (5·1 g., 3 mols.), the mixture heated on the steam-bath for 1 hour, and the product isolated as in the previous case. 1 : 2 : 3 : 8 : 9 : 10-Hexahydro-8-keto*cyclo*pent[*a*]indene (IV) was obtained as a pale yellow oil (1·34 g., 62%), b. p. 145°/12 mm., n_D^{17} 1·5740 (Found: C, 83·6; H, 7·1. Calc. for $C_{12}H_{12}O$: C, 83·7; H, 7·0%). The 2 : 4-dinitrophenylhydrazone separated from acetic acid as deep red needles, m. p. 214—215° (Found: C, 61·3; H, 4·4; N, 16·1. Calc. for $C_{18}H_{16}O_4N_4$: C, 61·4; H, 4·6; N, 15·9%) unaltered when mixed with the 2 : 4-dinitrophenylhydrazone of the ketone, m. p. 216—217°, prepared as described by Baker and Leeds (*loc. cit.*). The *oxime* of the ketone (IV) separated from dilute ethanol in colourless flakes, m. p. 117—119° (Found: C, 76·6; H, 7·0; N, 7·8. $C_{12}H_{13}ON$ requires C, 77·0; H, 7·0; N, 7·5%).

(b) *From* cyclo*pent*-1-*enecarboxyl chloride and benzene*. The acid chloride (95 g., 1 mol.) in dry benzene (900 c.c.) was cooled in ice, aluminium chloride (292 g., 3 mols.) added with shaking during ½ hour, the mixture heated on the steam-bath for 1 hour, and the ketone isolated next morning. The hexahydroketo*cyclo*pent[*a*]indene (IV), b. p. 145°/12 mm., was isolated as previously described, and obtained in a yield of 58% (73 g.); the 2 : 4-dinitrophenylhydrazone had m. p. and mixed m. p. 214—215°.

1-*Chloro*-2-*cyano*cyclo*pentane and* 2-*Chloro*cyclo*pentanecarboxyamide*.—These compounds were isolated in unsuccessful attempts to effect the addition of benzene to 1-cyano*cyclo*pentene. The cyano-compound (4·7 g.) and aluminium chloride (20 g.) in benzene (20 c.c.) and ether (100 c.c.) was treated with hydrogen chloride at 0°, and after 2 days at room temperature the mixture was heated on the steam-bath for ½ hour and poured on ice. The benzene layer was washed with dilute aqueous sodium hydroxide, dried ($MgSO_4$), and distilled, yielding 1-cyano*cyclo*pentene, b. p. 60—75°/18 mm. (1·35 g.), and 1-*chloro*-2-*cyano*cyclo*pentane*, b. p. 125—126°/18 mm. (Found: C, 56·0; H, 6·4; N, 10·7. C_6H_8NCl requires C, 55·6; H, 6·2; N, 10·8%). Hydrolysis of the chloro-compound (0·51 g.) with 10% aqueous sodium hydroxide for 4 hours on the steam-bath yielded *cyclo*pent-1-enecarboxylic acid (0·3 g.), m. p. and mixed m. p. 119—120°.

A similar experiment using anhydrous zinc chloride gave, on addition of a little ether to the products of reaction before final distillation, 2-*chloro*cyclo*pentanecarboxyamide* (0·42 g.) as a solid which separated from water in colourless flakes, m. p. 152—153° (Found: C, 49·1; H, 6·8; N, 9·6. $C_6H_{10}ONCl$ requires C, 48·9; H, 6·8; N, 9·5%). Distillation then yielded 1-chloro-2-cyano*cyclo*pentane (1·2 g.). Alkaline hydrolysis of this amide yielded *cyclo*pent-1-enecarboxylic acid.

1 : 2 : 3 : 8 : 9 : 10-*Hexahydro*cyclo*pent*[a]*indene* (V).—A solution of 1 : 2 : 3 : 8 : 9 : 10-hexahydro-8-keto*cyclo*pent[*a*]indene (IV) (10 g.) in toluene (10 c.c.) was added to amalgamated zinc (20 g.), water

(25 c.c.), and concentrated hydrochloric acid (50 c.c.), and the mixture stirred under reflux for 9 hours while heated in an oil-bath at 110—120°. More concentrated hydrochloric acid (5 c.c.) was added every 2 hours. The toluene layer was then shaken with aqueous sodium carbonate, dried ($MgSO_4$), and distilled, giving 1 : 2 : 3 : 8 : 9 : 10-*hexahydro*cyclo*pent*[a]*indene* (V) as a colourless oil (6·95 g., 76%), b. p. 73—75°/1 mm., 107—109°/12 mm., d_{54}^{24} 0·9962; n_D^{17} 1·5511 (Found : C, 91·5; H, 8·8. $C_{13}H_{14}$ requires C, 91·1; H, 8·9%).

This hydrocarbon was characterised as the *monosulphonamido*-derivative, in which substitution has probably occurred in position 6. Chlorosulphonic acid (5 c.c.) was slowly added at 0° with stirring to the hydrocarbon (V) (1·06 g.) in dry chloroform (10 c.c.). After an hour at room temperature the mixture was poured on ice, the chloroform layer was dried, and distilled, and the residual oil heated with powdered ammonium carbonate on the steam-bath for ½ hour. The material, soluble in dilute aqueous sodium hydroxide and precipitated by acid, was crystallised from benzene and then from dilute alcohol, giving minute crystals (0·16 g.), m. p. 130—131° (Found : C, 60·4; H, 6·3; N, 6·2; S, 13·2. $C_{13}H_{15}O_2NS$ requires C, 60·8; H, 6·3; N, 5·9; S, 13·5%).

1 : 2 : 3 : 8 : 9 : 10-*Hexahydro*-8-*hydroxy*cyclo*pent*[a]*indene* (VI).—The ketone (IV) (5 g.), anhydrous *iso*propyl alcohol (50 c.c.), and freshly distilled aluminium *iso*propoxide (5·95 g.) were heated on the steam-bath for 4 hours, whereafter acetone could no longer be detected in the distillate (for apparatus see "Organic Reactions," 1944, **2**, 198). Excess of alcohol was now evaporated off, water (60 c.c.) and concentrated hydrochloric acid (10 c.c.) added with ice-cooling, and the mixture extracted with ether. The extracts yielded a colourless oil (3·3 g.), b. p. 150—160°/18 mm., which contained a considerable amount of unchanged ketone (positive test with 2 : 4-dinitrophenylhydrazine). The crude oil (3·3 g.) in ethanol (25 c.c.) was boiled for 1 hour with glacial acetic acid (6 c.c.) and Girard reagent T (3·3 g.), poured into a solution of sodium carbonate (4·8 g.) in water (100 c.c.) and ice, and extracted with ether. The ether yielded an oil (2·3 g.) which gave a slight precipitate with 2 : 4-dinitrophenylhydrazine, but two further similar treatments with Girard reagent T gave a ketone-free oil (1·5 g.). This 1 : 2 : 3 : 8 : 9 : 10-hexahydro-8-hydroxy*cyclo*pent[*a*]indene (0·49 g.) (VI) gave an *α-naphthylurethane* derivative which separated after the alcohol had been heated with α-naphthyl *iso*cyanate (0·6 c.c.) and light petroleum (15 c.c.; b. p. 80—100°) for 2 hours on the steam-bath; the product (0·53 g.) recrystallised from light petroleum (b. p. 80—100°) or from dilute ethanol in needles, m. p. 152—156° (Found : C, 80·6; H, 6·5; N, 4·7. $C_{23}H_{21}O_2N$ requires C, 80·5; H, 6·1; N, 4·1%). The *p-nitrobenzoyl* derivative formed thin flakes, m. p. 98·5—99·5° (Found : C, 70·4; H, 5·3; N, 5·0. $C_{19}H_{17}O_4N$ requires C, 70·6; H, 5·3; N, 4·3%).

1 : 2 : 3 : 8 : 9 : 10-*Hexahydro*-8-*hydroxy*-8-*methyl*cyclo*pent*[a]*indene* (VII).—1 : 2 : 3 : 8 : 9 : 10-Hexahydro-8-keto*cyclo*pentindene (IV) (20 g.) in ether (20 c.c.) was added at 0° to a solution of the Grignard reagent prepared from magnesium (5·64 g.), methyl iodide (38 g.), and ether (100 c.c.). After being kept overnight the mixture was poured into dilute hydrochloric acid and ice, and the ethereal layer yielded a solid (19·1 g., 87%) which separated from light petroleum (b. p. 60—80°) in thick, hexagonal plates, m. p. 67—69° (Found : C, 82·9; H, 8·6. $C_{13}H_{16}O$ requires C, 83·0; H, 8·5%). This 1 : 2 : 3 : 8 : 9 : 10-*hexahydro*-8-*hydroxy*-8-*methyl*cyclo*pent*[a]*indene* (VII) appears to be dimorphic; when kept the crystals became opaque and then melted at 72—74°, but recrystallisation gave again the clear plates, m. p. 67—69°. The m. p. range of this apparently pure compound is doubtless connected with its dimorphism.

Dehydration of 1 : 2 : 3 : 8 : 9 : 10-*Hexahydro*-8-*hydroxy*-8-*methyl*cyclo*pent*[a]*indene* (VII). *Formation of* 1 : 2 : 3 : 8 : 9 : 10-*hexahydro*-8-*methylene*cyclo*pent*[a]*indene* (VIII).—The hydroxy-derivative (VII) (19·1 g.) was kept at 120° for 1 hour, then dissolved in ether, dried ($MgSO_4$), and distilled, finally over sodium, giving a colourless oil (10·9 g.), b. p. 90—92°/4 mm., n_D^{17} 1·5770 (Found : C, 91·6; H, 8·4. $C_{13}H_{14}$ requires C, 91·8; H, 8·2%). This hydrocarbon may not be homogeneous, but it is with little doubt essentially 1 : 2 : 3 : 8 : 9 : 10-*hexahydro*-8-*methylene*cyclo*pentindene* (VIII); it decolourises solutions of bromide in carbon tetrachloride and of potassium permanganate in water. Ozonolysis (of 0·39 g.) yielded a ketonic material giving a red 2 : 4-dinitrophenylhydrazone from ethanolic sulphuric acid solution (yield : 0·105 g., 13%), which after crystallisation from acetic acid formed dark red needles, m. p. 214—215°, undepressed when mixed with a specimen of the 2 : 4-dinitrophenylhydrazone of 1 : 2 : 3 : 8 : 9 : 10-hexahydro-8-keto*cyclo*pent[*a*]indene (IV).

9-*Bromo*-1 : 2 : 3 : 8 : 9 : 10-*hexahydro*-8-*keto*cyclo*pent*[a]*indene* (IX).—1 : 2 : 3 : 8 : 9 : 10-Hexahydro-8-keto*cyclo*pent[*a*]indene (IV) (18·3 g.) in acetic acid (50 c.c.) was gently heated on the steam-bath with bromine (18·7 g.) for ½ hour, then poured into water, and shaken with ether. The ethereal extract was washed with excess of aqueous sodium hydrogen carbonate, dried, and distilled, giving 9-*bromo*-1 : 2 : 3 : 8 : 9 : 10-*hexahydro*-8-*keto*cyclo*pent*[a]*indene* (IX) as a yellow oil (22·7 g., 85%), b. p. 125—127°/1 mm., n_D^{11} 1·6080 (Found : C, 57·6; H, 4·4. $C_{13}H_{11}OBr$ requires C, 57·4; H, 4·4%). The 2 : 4-*dinitrophenylhydrazone* separated from acetic acid in orange flakes, m. p. 197° (Found : C, 50·0; H, 3·6; N, 13·0. $C_{19}H_{15}O_4N_4Br$ requires C, 50·1; H, 3·5; N, 13·0%).

Reaction of 3-*Keto*-2-*phenyl*cyclo*pentane*-1-*carboxylic Acid* (X) *with Acetic Anhydride.*—(a) *Formation of* 3-*acetoxy*-2-*phenyl*cyclo*pent*-2-*ene*-1-*carboxylic acid* (XI). The keto-acid (X) (2 g.) in acetic anhydride (20 c.c.) was treated with a few drops of concentrated sulphuric acid, and after 22 hours at room temperature, the mixture was evaporated at 40° under diminished pressure, and the residue shaken with water and ether. The ethereal layer was dried ($MgSO_4$) and yielded an oil which was obtained crystalline from benzene–light petroleum (b. p. 60—80°). 3-*Acetoxy*-2-*phenyl*cyclo*pent*-2-*ene*-1-*carboxylic acid* (XI) separated as colourless needles (0·75 g.), m. p. 145° (Found : C, 68·3; H, 5·6. $C_{14}H_{14}O_4$ requires C, 68·3; H, 5·7%). This acid is precipitated unchanged after dissolving in dilute aqueous sodium hydrogen carbonate at 0°, but, when a solution in cold 5% aqueous sodium carbonate was acidified after being kept overnight, it regenerated 3-keto-2-phenyl*cyclo*pentane-1-carboxylic acid (X), m. p. and mixed m. p. 114—115°.

(b) 2 : 3′-*Diacetoxy*-2 : 3 : 4 : 5-*tetrahydro*-5-*keto*-2-*methyl*-3-*phenyl*cyclo*pent*-3-*eno*(2′ : 1′-3 : 4)*furan* (XIII). The keto-acid (X) (1 g.) and acetic anhydride (10 c.c.) were boiled for 12 hours, then evaporated under diminished pressure, and the residue crystallised from ethanol. The *acetoxy-lactone* (XIII) separated as thin plates (0·35 g.), m. p. 137—178° [Found: C, 65·7; H, 5·6; Ac, 24·9. $C_{14}H_{12}O_3(OAc)_2$ requires C, 65·5; H, 5·5; Ac, 26·1%].

5-*Keto*-4-*phenylhexane*-1 : 3-*dicarboxylic Acid*.—The preceding acetoxy-lactone (XIII) (0·2 g.) was boiled with 10% aqueous sodium hydroxide (4 c.c.) for ½ hour, the solution cooled and acidified, giving 5-*keto*-4-*phenylhexane*-1 : 3-*dicarboxylic acid* (XIV) as fine crystals, m. p. 154—155° [Found: C, 63·5; H, 6·5%; equiv., 126. $C_{12}H_{14}O(CO_2H)_2$ requires C, 63·6; H, 6·1%; equiv., 132]. When warmed with 10% aqueous sodium hydroxide, sodium hypochlorite, and potassium iodide, it readily gave a precipitate of iodoform, m. p. and mixed m. p. 119—120°.

2-*Phenyl*cyclo*pent*-2-*enone* (XV).—3-Keto-2-phenyl*cyclo*pentanecarboxylic acid (9 g.) was added with stirring to a previously prepared and cooled mixture of syrupy phosphoric acid (45 c.c.; *d* 1·75) and phosphoric anhydride (45 g.), and after 3 hours' heating on the steam-bath the product was cooled, poured on ice, and extracted with ether. The ethereal solution was washed with dilute aqueous sodium hydroxide, dried, and distilled, giving 2-*phenyl*cyclo*pent*-2-*enone* (XV) (3·1 g.) as an oil, b. p. 110—113°/2 mm., which solidified on cooling. It crystallised from light petroleum (b. p. 60—80°) as colourless plates, m. p. 72° (Found: C, 83·7; H, 6·3. $C_{11}H_{10}O$ requires C, 83·5; H, 6·3%). The 2 : 4-*dinitrophenylhydrazone* separated from dioxan in thick, orange-red needles, m. p. 209—210° (Found: C, 60·4; H, 4·2; N, 16·5. $C_{17}H_{14}O_4N_4$ requires C, 60·4; H, 4·1; N, 16·6%). The *semicarbazone* formed nacreous flakes from ethanol, m. p. 235—237° (decomp.) (Found: C, 66·6; H, 6·0; N, 19·4. $C_{12}H_{13}ON_3$ requires C, 67·0; H, 6·0; N, 19·5%). Oxidation of this ketone with alkaline potassium permanganate solution at the b. p. for ½ hour gave benzoic acid (49%), m. p. and mixed m. p. 122°.

2-*Phenyl*cyclo*pentanone* (XVI).—(a) *By reduction of* 2-*phenyl*cyclo*pent*-2-*enone* (XV). The ketone (XV) in methanol was shaken in hydrogen for 3 hours at one atm. pressure in presence of a small quantity of 30% palladium–charcoal, and the solution filtered and evaporated, leaving an oil which solidified at 0° but melted at room temperature. It yielded a 2 : 4-dinitrophenylhydrazone, m. p. 142—144° after crystallisation from ethanol; on admixture with the 2 : 4-dinitrophenylhydrazone prepared by method (b) the m. p. was 142—145°. The oxime formed colourless needles (from light petroleum), m. p. and mixed m. p. with the oxime prepared by method (b), 141—142°.

(b) *From* α-*phenyladipic acid* (XVII; R = H). α-Phenyladipic acid was prepared from the sodio-derivative of ethyl α-cyano-α-phenylacetate (Wallingford, Jones, and Homeyer, *J. Amer. Chem. Soc.*, 1942, **64**, 576; Horning and Finelli, *ibid.*, 1949, **71**, 3204) by reaction with 3-chloropropyl cyanide (*Org. Synth.*, 1944, Coll. Vol. I, p. 156). The sodio-derivative, prepared from sodium ethoxide (15·4 g.), phenylacetonitrile (26·2 g.), and ethyl carbonate (120 c.c.), was treated without isolation with 3-chloropropyl cyanide (23·2 g.), and the mixture heated in an oil-bath at 120° for 3 hours. The cooled, acidified product was extracted with ether, and the extracts were dried and distilled, giving a fraction (22·5 g.), b. p. 159—165°/1 mm., which was boiled with concentrated hydrochloric acid (150 c.c.) for 12 hours, then cooled, and the α-phenyladipic acid collected (19·5 g., 39%). It separated from water in colourless needles, m. p. 137—138° (Found: C, 65·2; H, 6·6. Calc. for $C_{12}H_{14}O_4$: C, 64·9; H, 6·3%) (Case, *J. Amer. Chem. Soc.*, 1933, **55**, 2929, records m. p. 131—133°, and Kuhn and Michel, *Ber.*, 1938, **71**, 1125, m. p. 135·5°). This acid (19·5 g.) was converted into the ethyl ester (XVII; R = Et), a very pale green oil (19·4 g.), b. p. 135—137°/0·5 mm., n_D^{15} 1·4932, by boiling it with ethanol (50 c.c.) and concentrated sulphuric acid (5 c.c.) for 6 hours, and working up the product in the usual way. Cyclisation of this ester (4·9 g.) was effected by boiling it for 6·5 hours with a solution of sodium (0·41 g.) in dry ethanol (12 c.c.), removing the ethanol by distillation, and hydrolysing and decarboxylating the product by boiling the residue with water (5 c.c.) and concentrated hydrochloric acid (15 c.c.) for 12 hours. The diluted mixture was then extracted with ether, and the extracts were washed with aqueous sodium carbonate, dried, and distilled, giving crude 2-phenyl*cyclo*pentanone (XVI) (1·35 g., 48%), collected at 114—124°/2 mm., which solidified on cooling. It separated from light petroleum (b. p. 60—80°) in colourless, thick plates, m. p. 38° (Found: C, 82·4; H, 7·5. Calc. for $C_{11}H_{12}O$: C, 82·5; H, 7·5%). The 2 : 4-*dinitrophenylhydrazone* formed orange needles, m. p. 146°, from ethanol (Found: C, 60·4; H, 4·8; N, 16·4. $C_{17}H_{16}O_4N_4$ requires C, 60·0; H, 4·7; N, 16·5%). The oxime separated from light petroleum (b. p. 60—80°) in silky needles, m. p. 141—142° (Found: C, 75·2; H, 7·2; N, 7·8. Calc. for $C_{11}H_{13}ON$: C, 75·4; H, 7·4; N, 8·0%). This ketone undergoes change on being kept; after 9 months a specimen had become sticky, and when washed with light petroleum left an insoluble residue, m. p. 110—114°. This observation may account for the erroneous m. p. of 126—127° recorded for this ketone by Mitchovitch (*Compt. rend.*, 1935, **200**, 1601); he gave m. p. 146° (decomp.) for the oxime, and m. p. 228° (decomp.) for the semicarbazone.

(c) *From* 2-*chlorocyclopentanone and phenylmagnesium bromide*. Repetition of this method of preparation described by Mitchovitch (*loc. cit.*) gave the ketone as an oil, b. p. 100—108°/2 mm., which partly solidified at 0°, but melted at room temperature; a crystalline oxime could not be obtained. The derived 2 : 4-dinitrophenylhydrazone had m. p. 144—145°, and the semicarbazone had m. p. 227—228°.

5-*Methyl*-2-*phenyl*cyclo*pentanone*.—Ethyl α-phenyladipate (8·9 g.; above) and a solution of sodium (0·74 g.) in anhydrous ethanol (20 c.c.) were boiled for 5·5 hours, to form the sodio-derivative of ethyl 2-keto-3-phenyl*cyclo*pentanonecarboxylate. Methyl iodide (6·8 g.) was then added and boiling continued for 2 hours, after which the mixture was evaporated and the residue boiled for 14 hours with water (35 c.c.) and concentrated hydrochloric acid (50 c.c.). The diluted solution was then extracted with ether, and the extracts were washed with aqueous sodium carbonate, dried and distilled, giving 5-*methyl*-2-*phenyl*cyclo*pentanone* as a colourless oil (2·1 g.), b. p. 91—93°/0·5 mm., n_D^{18} 1·5361 (Found: C, 82·5; H, 8·2. $C_{12}H_{14}O$ requires C, 82·8; H, 8·1%). The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate as yellow plates, m. p. 208° (Found: C, 60·9; H, 4·8; N, 5·6. $C_{18}H_{16}O_4N_4$ requires C, 61·0; H, 5·1; N, 15·8%).

Methyl 3-Keto-2-phenylcyclopentanecarboxylate.—3-Keto-2-phenylcyclopentanecarboxylic acid (X) (21·8 g.) was boiled for 4 hours with anhydrous methanol (100 c.c.) and concentrated sulphuric acid (6 c.c.), water added, and the solid *ester* collected and dried (20 g.). It separated from aqueous methanol in needles, m. p. 80° (Found: C, 72·0; H, 6·7. $C_{13}H_{14}O_3$ requires C, 71·6; H, 6·4%).

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172. *A New Reagent for the Oxidation of Acyloins to Diketones.*

By W. RIGBY.

Acyloins are efficiently oxidised to 1 : 2-diketones by heating them with bismuth oxide (Bi_2O_3) in solutions containing acetic acid, the oxide being reduced to the metal. The reagent is specific and the reaction often virtually quantitative: yields from the sensitive acyloins, furoin and piperoin, are better than those obtained by standard methods. The reaction serves as a qualitative test. The preparation of bismuth triacetate has been improved.

DURING an earlier investigation it was noticed that, when benzoin was oxidised at moderate temperatures by sodium bismuthate in acetic acid, the "normal" fission reaction occurred exclusively, but that, when the materials were boiled together, some metallic bismuth was precipitated. The presence of phosphoric acid prevented this further oxidation, even at the higher temperatures, and that was the reason for adding phosphoric acid to the acetic acid solution when acyloins were being oxidised (Rigby, *J.*, 1950, 1907). It was obvious that in the side-reaction the primary product of the bismuthate reduction, some compound of tervalent bismuth, was being further reduced.

It has now been found that acyloins are readily oxidised to 1 : 2-diketones by warming them, in media containing acetic acid, with bismuth oxide (Bi_2O_3) which is reduced to metallic bismuth; the reaction is smooth and rapid and appears to be specific for the $-CH(OH)\cdot CO-$ group of acyloins. Apart from its general utility, this mild, selective oxidising agent might have special value in the case of sensitive acyloins: it has been noted on several occasions that the usual copper reagents are not entirely satisfactory in all cases (cf., *e.g.*, Campbell, Dunsmuir, and Fitzgerald, *J.*, 1950, 2744). It is noteworthy that by the bismuth method piperil can be produced in almost quantitative yield—an improvement on the copper-catalysed ammonium nitrate–acetic acid reagent of Weiss and Appel (*J. Amer. Chem. Soc.*, 1949, **71**, 2269). Furil is obtained in 92% yield, compared with 63% by the copper–pyridine method (Hartmann and Dickey, *ibid.*, 1933, **55**, 1228), or 90% (m. p. 162°) by nitrobenzene (Nisbet, *J.*, 1928, 3124).

A convenient qualitative test for acyloins consists in heating, at 100° (or at its boiling point), a solution of *ca.* 0·1 g. of the substance in a few ml. of acetic acid with a little bismuth oxide, a black precipitate of finely divided bismuth being produced almost immediately.

For preparative purposes, acetic acid may be used alone as solvent; with use of a slight excess of the oxide, reaction then is complete in about 15—30 minutes at 95—100°, and yields are usually 90% or more; with benzoin, the oxidation is appreciable at about 70—75°. However, as some acyloins are discoloured slightly when heated with the undiluted acid, addition of technical 2-ethoxyethanol is desirable, although this slows the reaction somewhat; for the oxidation of furoin, dilution of the acetic acid with water was also effective in diminishing the marked discoloration which occurred under the usual conditions. Mineral acids or large amounts of water inhibit the reaction. Stirring the acyloin with a 20% excess of bismuth oxide in a mixture of acetic acid with 1—3 volumes of 2-ethoxyethanol at about 100° for 1½ hours gave the following % yields of diketone: benzil 96; anisil 95; piperil 97; furil 92. Isolation of the products is very simple. Typical aliphatic 1 : 2-diketones were readily obtained by an analogous procedure.

Presumably bismuth triacetate is formed initially and is the actual compound reduced: a solution of bismuth triacetate in acetic acid can be used instead of the extemporaneous mixture of oxide and acid, but normally offers no advantage, and the reaction is not appreciably more rapid. The triacetate is easily prepared and is stable under ordinary, good conditions of storage. It seems likely that union of the acyloin and bismuth compound through $-C-O-Bi$ linkages, perhaps involving the enediol, occurs before the oxidation.

While all the simple acyloins investigated readily reduce the bismuth oxide–acetic acid reagent, sugars gave no precipitate of bismuth; ascorbic acid also failed to reduce the reagent, and this was not due to its acidity as there was no reduction when sodium acetate was added. The simultaneous presence of glucose inhibits the reduction of bismuth oxide by benzoin in acetic acid unless an excess of the oxide is used; catechol has a similar effect, but resorcinol and quinol have not. It would appear that bismuth oxide reacts preferentially in the usual way with neighbouring hydroxyl groups of these polyhydroxy-compounds.

In order to examine the specificity of the reaction, various readily-oxidisable substances and substances showing some structural similarity to acyloins were heated with the bismuth oxide–acetic acid reagent: namely, hydrazine hydrate, formaldehyde, paraformaldehyde, metaldehyde, catechol (yellow solid produced), resorcinol, quinol, pyrogallol (yellow solid produced), *p*-phenylenediamine, ethyl lactate, pyruvic acid, glucose, sorbose, and diosphenol—but with negative results.

Experimental.

Bismuth Oxide.—Material of the ordinary laboratory grade was used : it was an impalpable yellow powder which lost 1·2% of its weight on ignition. A very old sample which had become almost white by exposure to air was unsatisfactory, as bismuth carbonate is not dissolved by hot acetic acid.

Bismuth Triacetate.—Bismuth oxide (50 g.) was heated at 140—150° with acetic acid (300 ml.) and acetic anhydride (35 ml.) until it dissolved (1½—2 hours), to leave only a light suspension of (presumably) the small amount of carbonate contaminant. After filtration, the triacetate separated on cooling as glistening, colourless, elongated six-sided tablets (75 g., 90%) [Found : Bi (by ignition after moistening with concentrated nitric acid), 54·4. Calc. for $BiC_6H_9O_6$: Bi, 54·1%]. The substance is insoluble in, and hydrolysed by, water, but is soluble in aqueous acetic acid of above *ca.* 60% strength; it is insoluble (milky) in alcohol or 2-ethoxyethanol. The acetic acid can easily be driven off by gentle heating with concentrated nitric acid before ignition; the material then ignites to oxide without trouble. Ignition before removal of the acetic acid entails volatilisation of bismuth, but Salkowsky's procedure (*Biochem. Z.*, 1917, **79**, 99) appears to be unnecessary and undesirable.

General Procedures.—(a) *In the mixed solvent.* To a briskly stirred solution of the acyloin in a mixture of acetic acid with ½—3 volumes of technical 2-ethoxyethanol, heated at 105—110°, was added 1·2 times the theoretical amount of bismuth oxide, and stirring and heating were continued for 70—80 minutes : as wide-mouthed open flasks were used, the temperature in the reaction mixture was a few degrees lower than the bath-temperature; the initially black precipitate was partly converted (by oxidation) into a yellowish suspension before the end of the experiment. The mixture was then heated to boiling and filtered, and on cooling deposited the major part of the diketone, which was removed (ice-cooling brought about some contamination with bismuth compounds). The filtrate was distilled to dryness from the water-bath under reduced pressure, the residue was boiled with benzene, and the hot benzene solution clarified by filtration through 2 g. of aluminium oxide which removed residual traces of bismuth compounds. Evaporation to low bulk allowed the remainder of the diketone to crystallise. The solutions and products had the clear yellow colour of the pure diketone (except furil, which in the crude state was slightly discoloured).

(b) *In acetic acid alone.* The acyloin, dissolved in 2—5 times its weight of acetic acid, was similarly treated with 1·2 times the theoretical quantity of bismuth oxide; 15—30 minutes' stirring usually sufficed for a mixture heated in a water-bath. After filtration from bismuth, the diketone deposited at room temperature was removed and the filtrate, after addition of water (¾ the volume of the acetic acid used), was extracted with a similar quantity of benzene; alternatively, the whole of the original hot filtrate was extracted with warm benzene after the addition of warm water. After being washed with water and filtered through 2 g. of aluminium oxide, the benzene solution was concentrated and a further crop of diketone crystallised. The solutions and crude products had a slight orange tint instead of the yellow of the pure diketone, and the yields were usually a few per cent. lower than when the mixed solvent was used.

Benzil.—Benzoin (10·6 g.) with acetic acid (10 ml.), 2-ethoxyethanol (15 ml.), and bismuth oxide (9·3 g.) (internal temp. 104°; 1 hour) gave benzil, m. p. 95° (10·1 g., 95%). Benzoin (10·6 g.) with acetic acid (22 ml.) and bismuth oxide (9·3 g.) (95—97°; 30 minutes) gave benzil (9·8 g., 93%; an orange-coloured syrup from which benzoic acid could be isolated remained after the crystallisations. An analogous experiment in which a hot solution of bismuth triacetate (15 g.) in acetic acid (45 ml.) was used gave a similar result.

Anisil.—Anisoin (4·7 g.) with acetic acid (9 ml.), 2-ethoxyethanol (18 ml.), and bismuth oxide (3·7 g.) (105°; 1 hour) gave anisil, m. p. 133° (4·42 g., 95%), 87% being obtained in the first crystallisation. Anisoin (12·4 g.) with acetic acid (40 ml.) and bismuth oxide (9·3 g.) (100°; 20 minutes) gave anisil (91%), a little anisoin remaining. There was only slight discoloration.

Piperil.—Piperoin (3·75 g.) with acetic acid (8 ml.), 2-ethoxyethanol (24 ml.), and bismuth oxide (2·4 g.) (103—105°; 1½ hours) gave piperil, m. p. 173—174° (3·63 g., 97%), 92% being obtained in the first crystallisation : even the evaporated liquors were barely discoloured. (Weiss and Appel, *loc. cit.*, report an 89% yield on oxidation by ammonium nitrate–copper acetate.)

Furil.—Furoin (2·4 g.) with acetic acid (8 ml.), 2-ethoxyethanol (24 ml.), and bismuth oxide (2·4 g.) (water-bath; ¾ hour) gave furil, m. p. 166° (2·2 g., 92%), 84% being obtained in the first crystallisation. Furoin (5·1 g.) with acetic acid (30 ml.), water (15 ml.), and bismuth oxide (5·1 g.) (water-bath; 10

minutes) gave furil (4·5 g., 88%); the crude product was only slightly discoloured. Undiluted acetic acid at 80—85° gave an inferior product (79%), and at 100° the initial product was bronze-coloured. Hartmann and Dickey (*loc. cit.*) reported a 63% yield by the copper–pyridine method, and their initial crude product was described as black.

Diacetyl.—A mixture of commercial acetoin (a light brown syrup) (22 g.), acetic acid (35 ml.), and bismuth oxide (40 g.) was distilled from an oil-bath through a small Fenske column, with a variable-ratio take-off head, at atmospheric pressure until the distillate was no longer yellow, the distillation temperature being finally allowed to rise to 107°. The distillate (*ca.* 35 g.) was redistilled, through the same column, whereupon fractionation was much more effective; practically the whole of the diacetyl distilled as an azeotrope at *ca.* 79·5° (presumably owing to water present in the starting material) and this, together with the next approx. 2 ml. which distilled up to about 100° and accounted for all the remaining yellow material, was dried ($CaCl_2$) and redistilled in the same apparatus, the fraction boiling at 89—91° being collected (yield, 12·5 g.). Condensation with *o*-phenylenediamine gave 2 : 3-dimethylquinoxaline, double m. p. 85° and 107°. No attempt was made to improve the yield by varying the experimental conditions as had been done in the case of furil; the purity of the starting material was unknown.

Octane-4 : 5-dione.—Butyroin, b. p. 80—86°/12 mm. (*Org. Synth.*, **13**, 24) (21·6 g.), acetic acid (75 ml.), and bismuth oxide (25 g.) were stirred together in a boiling water-bath for 15 minutes, and bismuth and its compounds were filtered off. Removal of the acetic acid by distillation was unsatisfactory, appreciable amounts of the volatile ketone being carried over with it; accordingly the acetic acid solution was diluted with its own volume of water and extracted with benzene. After washing of the solution with water the benzene was very easily removed under reduced pressure, and the octanedione collected at 94—95°/65 mm. (13·8 g.). A colourless residue remained. The product, on condensation with *o*-phenylenediamine, gave 2 : 3-di-*n*-propylquinoxaline, m. p. 44° (lit., 42·9°). A sample of the starting material on careful fractionation yielded 84% of material distilling within the ranges of octanedione (of which a few per cent. was present) and butyroin. No attempt was made to improve the yield of the oxidation reaction by varying the conditions.

Qualitative Tests.—Approx. 0·1 g. of the substance was gently boiled with acetic acid (2—3 ml.) and bismuth oxide (*ca.* 0·1 g.). With resorcinol, quinol, 40% formaldehyde, paraformaldehyde, metaldehyde, ethyl lactate, pyruvic acid, ascorbic acid, diosphenol, *p*-phenylenediamine, and hydrazine hydrate there was no visible change; catechol and pyrogallol gave yellow precipitates of (presumably) the bismuth derivative; the glucose solution gradually became light brown on continued boiling—there was no precipitate—L-sorbose reacted similarly but rather more rapidly; a mixture of glucose (*ca.* 0·1 g.) and benzoin (0·05 g.) in acetic acid (2—3 ml.) with bismuth oxide (*ca.* 0·02 g.) gave only a slight turbidity of bismuth on boiling, but on further addition of bismuth oxide (*ca.* 0·1 g.) more bismuth was precipitated; addition of bismuth oxide to a boiling solution of catechol (0·1 g.) with benzoin (*ca.* 0·05 g.) in acetic acid gave at first only a precipitate of the yellow bismuth–catechol compound, but further additions of bismuth oxide in excess of that required by the catechol resulted in reduction to metallic bismuth.

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173. *Carcinogenic Nitrogen Compounds. Part VI. Derivatives of* 1 : 2- *and* 3 : 4-*Benzophenarsazines.*

By NG. PH. BUU-HOÏ and RENÉ ROYER.

In continuation of earlier research, a series of new 10-chloro-, 10-alkyl-, and 10-aryl-5 : 10-dihydro-1 : 2- and -3 : 4-benzophenarsazines has been prepared by known methods for biological testing as potential carcinogens, fungicides, and chemotherapeutic agents. During this study, several new diarylamines were prepared.

OF the cancers produced by definite chemical substances, those evoked by arsenic compounds have been the most often studied, except for those produced by polycyclic hydrocarbons, amines, and azo-dyes. However, the carcinogenic properties of arsenic have so far been demonstrated only for its inorganic derivatives such as arsenic trioxide, arsenious acid, and arsenites (see Lacassagne, " Les cancers produits par des substances chimiques exogènes," 1946, Paris, p. 5). Very few organic arsenicals have as yet been tested. Hval (quoted by Hartwell, " Survey of Compounds which have been tested for Carcinogenic Activity," 1941, Washington, p. 310) used neoarsphenamine in subcutaneous injections, with negative results; Visser and ten Seldam (*Geneesk. tijdschr. Nederl.-Indië*, 1938, **78**, 3280) obtained no cancers from 10-chloro-5 : 10-dihydrophenarsazine, diphenylchloroarsine, and diphenylcyanoarsine in skin-painting tests, but some papillomas with the last two compounds.

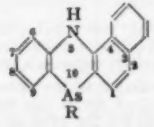
However, in these researches the short duration of the experiments (140 days in the case of Hval and 5 months in that of Visser and ten Seldam) is likely to invalidate any conclusion

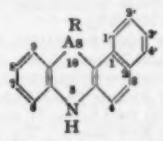
concerning inactivity. Furthermore, the high degree of structural specificity in neighbouring groups of carcinogenic hydrocarbons, amines, and azo-dyes suggests that large series of organic arsenicals should be tested before any definite conclusions are elaborated.

This paper deals with the synthesis of a wide series of derivatives of 5 : 10-dihydro-3 : 4- (I) and -1 : 2-benzophenarsazines (II), and is part of a broad investigation of organic arsenicals. Renewed incentive for such research has been offered by Ludford's work (*Arch. exp. Zellforsch.*, **1936**, **18**, 411) on cacodylic acid, and that of King and Ludford (*J.*, 1950, 2086) on various

Substituent.	Decomp. above :	M. p.	Formula.	Found, %. C.	Found, %. H.	Reqd., %. C.	Reqd., %. H.
10-*Chloro*-5 : 10-*dihydro*-3 : 4-*benzophenarsazines* (I ; R = Cl).							
7 : 9-Dimethyl	275°	312—314°	$C_{16}H_{15}NClAs$	60·9	4·0		
6 : 9-Dimethyl	206	217	$C_{16}H_{15}NClAs$	60·5	4·5		
6 : 8-Dimethyl	215	244	$C_{16}H_{15}NClAs$	60·8	4·4	60·7	4·2
7 : 8-Dimethyl	253	280	$C_{16}H_{15}NClAs$	61·0	4·2		
6 : 7-Dimethyl	230—235	260	$C_{16}H_{15}NClAs$	61·0	4·0		
6-Methyl-9-*iso*propyl	208	230	$C_{20}H_{19}NClAs$	62·3	5·0	62·5	4·9
7-Chloro-6-methyl	240	275—280	$C_{17}H_{12}NCl_3As$	54·0	3·2	54·2	3·2
8-Chloro	206	221—222	$C_{16}H_{10}NCl_3As$	53·2	3·0	53·0	2·7
8-1′-Methyl-*n*-butyl	160	165	$C_{21}H_{21}NClAs$	63·2	5·6	63·4	5·3
8-(1 : 1-Dimethyl-*n*-propyl)	190	199	$C_{21}H_{21}NClAs$	63·1	5·2	,,	,,
8-Phenyl	255	275	$C_{24}H_{15}NClAs$	65·0	3·6	65·4	3·7
6-Phenyl	181	195	$C_{22}H_{15}NClAs$	65·1	3·8	,,	,,
8-Methoxy	220	242	$C_{17}H_{12}ONClAs$	57·2	3·3	57·0	3·6
6-Methoxy	215	239	$C_{17}H_{12}ONClAs$	57·1	3·5	,,	,,
6-Ethoxy	190	204	$C_{18}H_{14}ONClAs$	58·3	4·1	58·1	4·0
10-*Chloro*-5 : 10-*dihydro*-1 : 2-*benzophenarsazines* (II ; R = Cl).							
7 : 9-Dimethyl	275	314	$C_{16}H_{15}NClAs$	60·4	4·0		
6 : 9-Dimethyl	220	250	$C_{16}H_{15}NClAs$	60·6	4·2	60·7	4·2
6 : 7-Dimethyl	235	249	$C_{16}H_{15}NClAs$	60·4	4·4		
7 : 8-Dimethyl	250	285	$C_{16}H_{15}NClAs$	60·8	4·0		
6-Methyl-9-*iso*propyl	220	265	$C_{20}H_{19}NClAs$	62·6	5·2	62·5	4·9
8-Chloro	240	262	$C_{16}H_{10}NCl_3As$	53·3	2·9	53·0	2·7
7-Chloro-6-methyl	270	290	$C_{17}H_{12}NCl_3As$	53·9	3·0	54·2	3·2
8-1′-Methyl-*n*-butyl	165	174	$C_{21}H_{21}NClAs$	63·0	5·5	63·4	5·3
8-(1 : 1-Dimethyl-*n*-propyl)	210	228	$C_{21}H_{21}NClAs$	63·2	5·5	,,	,,
8-Phenyl	245	260—265	$C_{22}H_{15}NClAs$	65·2	3·5	65·4	3·7
6-Phenyl	215	242	$C_{22}H_{15}NClAs$	65·1	3·8	,,	,,
8-Methoxy	233—235	245	$C_{17}H_{12}ONClAs$	56·5	3·8	57·0	3·6
6-Ethoxy	170	192	$C_{18}H_{14}ONClAs$	57·7	4·1	58·1	4·0
3′-*tert.*-Butyl-8-methyl	268	271	$C_{21}H_{21}NClAs$	63·0	5·4	63·4	5·3
5 : 10-*Dihydro*-3 : 4-*benzophenarsazines* (I).							
7 : 9 : 10-Trimethyl		121	$C_{18}H_{18}NAs$	68·0	5·6		
6 : 9 : 10-Trimethyl		110	$C_{18}H_{18}NAs$	67·8	5·2		
6 : 7 : 10-Trimethyl		130	$C_{18}H_{18}NAs$	67·7	5·5	68·0	5·4
6 : 8 : 10-Trimethyl		92	$C_{18}H_{18}NAs$	68·2	5·6		
7 : 8 : 10-Trimethyl		171	$C_{18}H_{18}NAs$	68·3	5·1		
8-Chloro-10-methyl		123	$C_{17}H_{15}NClAs$	59·4	3·7	59·7	3·8
8-Chloro-10-ethyl		81	$C_{18}H_{15}NClAs$	60·5	4·4	60·7	4·2
10-Ethyl-6 : 9-dimethyl		109	$C_{20}H_{20}NAs$	68·8	5·9	68·7	5·7
10-Benzyl-6 : 9-dimethyl		174	$C_{25}H_{22}NAs$	72·4	5·1	72·9	5·0
5 : 10-*Dihydro*-1 : 2-*benzophenarsazines* (II).							
7 : 8 : 10-Trimethyl		142	$C_{18}H_{18}NAs$	68·2	5·5		
6 : 9 : 10-Trimethyl		138	$C_{18}H_{18}NAs$	68·4	5·4	68·0	5·4
6 : 7 : 10-Trimethyl		137	$C_{18}H_{18}NAs$	68·2	5·2		
10-Ethyl-7 : 9-dimethyl		104	$C_{20}H_{20}NAs$	68·4	5·8	68·7	5·7
10-Ethyl-6 : 7-dimethyl		128	$C_{20}H_{20}NAs$	68·6	5·6	,,	,,
7 : 8-Dimethyl-10-*iso*propyl		dec. >180	$C_{21}H_{22}NAs$	69·3	5·7	69·4	6·0
7-Chloro-6 : 10-dimethyl		143	$C_{18}H_{16}NClAs$	60·9	4·0	60·7	4·2
7-Chloro-10-ethyl-6-methyl		110	$C_{19}H_{17}NClAs$	61·4	4·8	61·6	4·6
10-*n*-Butyl-7-chloro-6-methyl		105	$C_{21}H_{21}NClAs$	63·5	5·4	63·3	5·3
10-Methyl-8-1′-methyl-*n*-butyl		101	$C_{22}H_{24}NAs$	69·7	6·5	70·0	6·3
10-Methyl-8-(1 : 1-dimethyl-*n*-propyl)		151	$C_{23}H_{24}NAs$	70·3	6·1	,,	,,
8-Methoxy-10-methyl		158	$C_{18}H_{16}ONAs$	64·3	4·6	64·0	4·7
10-Methyl-8-phenyl		189	$C_{25}H_{18}NAs$	72·4	4·4	72·0	4·7
10-Methyl-6-phenyl		135	$C_{25}H_{18}NAs$	72·0	4·8	,,	,,
10-Ethyl-6-phenyl		116	$C_{24}H_{20}NAs$	72·3	5·2	72·5	5·0
6 : 10-Diphenyl		162	$C_{24}H_{20}NAs$	75·8	4·5	75·5	4·5

alkyl- and aryl-arsonic acids and 3-(1-phenylethylamino)propylarsine dichloride as potent mitotic poisons.

(I.) 

 (II.)

The angular benzophenarsazines were chosen because of their molecular kinship with 1 : 2- and 3 : 4-benzacridines and 1 : 2- and 3 : 4-benzocarbazoles, in which groups several carcinogens have already been detected (Lacassagne, Buu-Hoï, Lecocq, and Rudali, *Bull. Cancer*, 1946, **33**, 48; 1947, **34**, 22; Lacassagne, Buu-Hoï, and Zajdela, *Compt. rend. Soc. Biol.*, 1947, **141**, 635). The Wieland–Rheinheimer reaction of arsenic trichloride with secondary diarylamines (*Annalen*, 1921, **423**, 1) has already been used for the preparation of 10-chloro-5 : 10-dihydro-1 : 2- and -3 : 4-benzophenarsazine (Lewis and Hamilton, *J. Amer. Chem. Soc.*, 1921, **43**, 2219; Burton and Gibson, *J.*, 1926, 2243), and of several of their functional derivatives (Buu-Hoï, Hiong-Ki-Weï, and Royer, *Compt. rend.*, 1945, **220**, 50; *Rev. scientif.*, 1944, **82**, 453; 1945, **83**, 41). A number of new 10-chloro-5 : 10-dihydro-1 : 2- and -3 : 4-benzophenarsazines bearing alkyl, alkyloxy-, and halogen substituents in various positions have now been similarly synthesised (see Table). Several new *N*-arylnaphthylamines used were prepared by the Knoevenagel reaction (*J. pr. Chem.*, 1914, **89**, 17); however, an attempt to prepare *N*-*p*-bromophenyl-α-naphthylamine from *p*-bromoaniline and α-naphthylamine by this reaction resulted in a complete removal of the nuclear halogen at relatively low temperature; this is similar to Knoevenagel's observation (*loc. cit.*) that *N*-*p*-chlorophenyl-α-naphthylamine could not be prepared from α-naphthol and *p*-chloroaniline.

The 10-chloro-5 : 10-dihydro-1 : 2- and -3 : 4-benzophenarsazines were yellow to orange substances with high melting points, which did not lend themselves to *N*-nitrosation, a peculiarity that had previously been observed in the case of 10-chloro-5 : 10-dihydrophenarsazine (Rasuwajew and Godina, *Ber.*, 1932, **65**, 666).

The action of alkyl- or aryl-magnesium halides on 10-chloro-5 : 10-dihydro-1 : 2- and -3 : 4-benzophenarsazines readily replaced the 10-chlorine atom by alkyl or aryl (cf. Seide and Gorski, *Ber.*, 1929, **62**, 2186; Buu-Hoï and Royer, *loc. cit.*). The new 10-alkyl- and 10-aryl-5 : 10-dihydro-1 : 2- and -3 : 4-benzophenarsazines thus obtained are listed in the Table.

The tests for carcinogenicity of 10-chloro-5 : 10-dihydro-1 : 2- and -3 : 4-benzophenarsazines (performed in this Institute by Dr. G. Rudali under Professor A. Lacassagne) are not yet complete and will be reported later. The widespread epilation and papillomas obtained so far in painting tests suggest activity in a few of these compounds; no such reactions are to be observed with the corresponding 10-alkyl compounds. Similarly, tests for fungicidal properties showed notable activity against *Fusarium graminearum* in the group of 10-chloro-5 : 10-dihydro-1 : 2- and -3 : 4-benzophenarsazines, but none in that of 10-alkyl compounds. On the other hand, several of the latter inhibit the growth of *Staphylococcus aureus* at a concentration of $\sim 10^{-5}$. Details will be published elsewhere.

Experimental.

[With J. F. Miquel and M. Hubert-Habart.]

N-(3 : 5-*Dimethylphenyl*)-α-*naphthylamine*.—A mixture of *s*-*m*-xylidine (10 g.), α-naphthol (12 g.), and iodine (0·2 g.) was heated under reflux for 20 hours, water being copiously evolved. The dark oil obtained was dissolved in toluene, washed with aqueous sodium hydroxide, and dried (Na_2SO_4); after removal of the solvent, the residue was vacuum-distilled, giving *N*-(3 : 5-*dimethylphenyl*)-α-*naphthylamine*, b. p. 255—257°/16 mm. (8 g.), crystallising from ligroin in shiny colourless needles, m. p. 52° (Found : N, 5·7. $C_{18}H_{17}N$ requires N, 5·6%). The use of α-naphthylamine in place of α-naphthol (cf. Knoevenagel, *loc. cit.*) for the preparation of this amine is not advisable, since it gave a product containing much di-α-naphthylamine.

N-(2-*Methyl*-5-iso*propylphenyl*)-α-*naphthylamine*, similarly obtained from 2-aminocymene (8 g.), α-naphthol (12 g.), and iodine (0·2 g.) (yield, 8 g.), was a viscous pale yellow oil, b. p. 258—260°/20 mm. (Found : N, 5·0. $C_{20}H_{21}N$ requires N, 5·1%).

N-(*p*-1-*Methylbutylphenyl*)-α-*naphthylamine* was obtained from *p*-1-methylbutylaniline (10 g.), α-naphthol (10 g.), and iodine (0·2 g.) as a pale yellow viscous oil (10 g.), b. p. 270—275°/20 mm. (Found : N, 4·8. $C_{21}H_{23}N$ requires N, 4·8%).

N-2-*Diphenylyl*-α-*naphthylamine*, from 2-aminodiphenyl (20 g.), α-naphthol (23 g.), and iodine (0·3 g.), formed, from ethanol, silky colourless needles (8 g.), m. p. 127°, b. p. 295—298°/28 mm. (Found : N, 4·5. $C_{22}H_{17}N$ requires N, 4·7%).

N-o-*Ethoxyphenyl*-α-*naphthylamine*, from *o*-phenetidine (15 g.), α-naphthol (20 g.), and iodine (0·2 g.), was a pale yellow viscous oil, b. p. 257—260°/21 mm. (Found: N, 5·0. $C_{18}H_{17}ON$ requires N, 5·3%). The isomeric N-o-*ethoxyphenyl*-β-*naphthylamine* obtained from *o*-phenetidine and β-naphthol crystallised from ligroin or methanol in fine shiny colourless needles, m. p. 82—83° (Found: N, 5·2. $C_{18}H_{17}ON$ requires N, 5·3%).

N-p-*Tolyl*-6-tert.-*butyl*-2-*naphthylamine*, from *p*-toluidine (10 g.), 6-*tert.*-butyl-2-naphthol (Buu-Hoï, Le Bihan, Binon, and Rayet, *J. Org. Chem.*, 1950, **15**, 1060) (15 g.), and iodine (0·2 g.), formed, from methanol, shiny colourless prisms, m. p. 99° (Found: N, 4·6. $C_{21}H_{23}N$ requires N, 4·8%).

Condensation of Arsenic Trichloride with Diarylamines.—A solution of the appropriate diarylamine (1 mol.) and arsenic trichloride (1 mol.) in *o*-dichlorobenzene (5—6 times the weight of amine) was gently refluxed for 6—8 hours. The reaction could be perceived by the gradual change of colour to yellow. After cooling, the chloroarsine generally crystallised, and was collected, washed with benzene, and recrystallised from an appropriate solvent (chlorobenzene or *o*-dichlorobenzene). In some cases (*e.g.*, the amyl derivatives) concentration of the reaction mixture was necessary in order to bring about crystallisation; light solvents (benzene, toluene) were then used for purification. The 10-chloro-5 : 10-dihydro-1 : 2- and -3 : 4-benzophenarsazines thus obtained were well-formed greenish to orange-yellow needles, giving orange to red colours with sulphuric acid. They were best characterised by a point of commencing decomposition as well as by the real m. p.

Action of Grignard Reagents on 10-*Chloro*-5 : 10-*dihydro*-1 : 2- *and* -3 : 4-*benzophenarsazines.*—The finely powdered and well-dried chloroarsine (1 mol.) was cautiously added, in small portions, to an ethereal solution of the appropriate alkyl- or aryl-magnesium compound (2·5 mols.), with frequent shaking. A lively reaction generally set in, with gradual disappearance of the insoluble chloroarsine; after 15 minutes' refluxing on a water-bath, the mixture was decomposed with ice-cooled aqueous ammonium chloride, the ether allowed to evaporate, and the residue recrystallised from ethanol, ligroin, or acetone. All the arsines thus obtained were colourless or faintly yellow needles, giving with sulphuric acid yellow, orange, or brown-red halochromic colours.

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174. *The Fluorination of Compounds of Vanadium, Chromium, and Manganese by Bromine Trifluoride.*

By A. G. Sharpe and A. A. Woolf.

New complex fluorides $KCrOF_4$, $AgCrOF_4$, and $KMnF_5$ are obtained by the action of bromine trifluoride on potassium dichromate, silver dichromate, and potassium permanganate; all are readily hydrolysed. Unsuccessful attempts to prepare manganese tetrafluoride are described; quadrivalent manganese is, however, stabilised in bromine trifluoride, as in aqueous solvents, by complex formation, yielding, *e.g.*, $KMnF_5$ and K_2MnF_6. Removal of oxygen from vanadium pentoxide and vanadates by bromine trifluoride is usually slow, and owing to the formation of oxygen-containing complexes these substances are not suitable starting materials for the preparation of hexafluorovanadates; nitrosonium hexafluorovanadate is, however, obtained from nitrosyl chloride, vanadium pentoxide, and bromine trifluoride.

Preliminary experiments on the action of bromine trifluoride on chromium compounds were made in this laboratory by Banks (Thesis, Cambridge, 1948), who showed that this reagent converts chromium trioxide and potassium dichromate into oxygen- and fluorine-containing chromium compounds in an oxidation state between four and six. This paper describes detailed work on these reactions and those of compounds of vanadium and manganese; the principles and technique of the preparation of complex fluorides by bromine trifluoride have previously been discussed (Woolf and Emeléus, *J.*, 1949, 2865; Sharpe, *J.*, 1950, 3444).

Emeléus and Gutmann (*J.*, 1949, 2979) showed that bromine trifluoride, vanadium trichloride, and alkali-metal halides yield hexafluorovanadates, *e.g.*, KVF_6. When bromine trifluoride reacts with vanadium pentoxide, however, the volume of oxygen evolved, measured by Emeléus and Woolf's method (*J.*, 1950, 164), corresponds to only three atoms of oxygen per molecule of the pentoxide. The composition of the product from sodium vanadate varies from $NaVOF_4$ to $NaVF_6$ according to the time for which the vanadate is boiled with bromine trifluoride. Similar results were obtained with other vanadates. In view of the difficulty of determining combined oxygen, it is inadvisable to replace vanadium trichloride by the pentoxide or an oxy-salt in the preparation of hexafluorovanadates.

Chromium trioxide reacts with bromine trifluoride with liberation of two-thirds of its oxygen. The residue slowly volatilises *in vacuo* at temperatures necessary for removal of the excess of

bromine trifluoride, and the isolation of a chromium oxyfluoride has not been achieved. If, however, the solution obtained from chromium trioxide and bromine trifluoride is treated with one mole of a "base" on the bromine trifluoride system (*e.g.*, $KBrF_4$, $AgBrF_4$) complex oxyfluorides of quinquevalent chromium are obtained. The action of bromine trifluoride on a mixture of potassium chloride and chromium trioxide in equimolecular proportions, for example, yields a residue of composition $KCrOF_4.0{\cdot}5BrF_3$ if the solution is evaporated *in vacuo* at 20°; heating at 130—150° effects removal of all the combined bromine trifluoride, and potassium tetrafluoro-oxychromate(v), $KCrOF_4$, remains. This substance is also produced by fluorination of potassium dichromate with bromine trifluoride, five-sevenths of the oxygen initially present being eliminated. It is immediately hydrolysed by water, forming a solution containing ter- and sexa-valent chromium in 1 : 2 proportion. The corresponding silver salt, $AgCrOF_4$, is similarly obtained from silver dichromate; a pure nitrosonium salt could not be made. Potassium chromate and bromine trifluoride appear to yield a mixture of potassium tetrafluoro-oxychromate(v) and tetrafluorobromite: there is no evidence for the formation of another complex, K_3CrOF_5, although this would be more likely to contain six-co-ordinated chromium. Thus the valency of chromium in complex halide ions decreases with decreasing oxygen content: potassium fluorotrioxychromate(vi), $KCrO_3F$, is well known, but the highest complex fluoride is K_2CrF_6 (Huss and Klemm, *Z. anorg. Chem.*, 1950, **262**, 25).

Recent work on manganese fluorides has been reported by Aynsley, Peacock, and Robinson (*J.*, 1950, 1622) and by Huss and Klemm (*loc. cit.*). The former authors state that fluorine and potassium permanganate at 150° yield a mixture of potassium, manganese(II), and manganese(III) fluorides, but no potassium hexafluoromanganite(IV), K_2MnF_6; the latter authors obtained the hexafluoromanganite by heating a mixture of composition $2KCl : MnCl_2$ in fluorine.

Manganous iodate reacts vigorously with bromine trifluoride, with evolution of all the oxygen and formation of iodine pentafluoride. The solution which remains contains quadrivalent manganese, as is shown by its successive conversion into the complex fluorides $KMnF_5$ and K_2MnF_6 by treatment with potassium tetrafluorobromite in pure (pale yellow) bromine trifluoride: in these reactions, no bromine is liberated. Since any increase in the oxidation number of the manganese would require simultaneous reduction of some bromine trifluoride to bromine (readily detectable by its colour) the manganese must be in the oxidation state +4 throughout. From the solution, however, isolation of manganese tetrafluoride is impossible: the unstable addition product, probably $(BrF_3)(MnF_5)$, decomposes when gently heated, and removal of the bromine trifluoride yields only a residue of manganese trifluoride.

A more convenient preparation of potassium pentafluoromanganite(IV), $KMnF_5$, is from potassium permanganate and bromine trifluoride. Oxygen evolution from the permanganate is quantitative, and removal of the solvent *in vacuo* leaves the fluoromanganite as a pinkish powder which is decomposed by water with the production of hydrated manganese dioxide and hydrofluoric acid. *X*-Ray powder photography shows its freedom from KF, MnF_3, and K_2MnF_6. Fluorination of a mixture of equimolecular proportions of potassium permanganate and potassium chloride with bromine trifluoride yields yellow potassium hexafluoromanganite(IV), and there are thus two complex fluorides of potassium and quadrivalent manganese.

Treatment of dinitrogen tetroxide and manganous iodate with bromine trifluoride, in the way used by Woolf and Emeléus (*J.*, 1950, 1050) for the preparation of nitronium complex fluorides, yielded a nitrogen-containing product which was probably an impure nitronium fluoromanganite: its thermal decomposition at 150° again yielded only manganese trifluoride. Manganese trifluoride is found by *X*-ray powder photography to be isomorphous with cobalt trifluoride and hence with the other trifluorides of metals of the first transition series.

The failure to prepare manganese tetrafluoride strongly suggests that quadrivalent manganese is stable in bromine trifluoride only when in a complex anion. This recalls the similar stability in aqueous solvents: quadrivalent manganese appears only in very sparingly soluble compounds (*e.g.*, MnO_2) or in complex ions (*e.g.*, MnF_6^{--}, $MnCl_6^{--}$, and $Mn(CN)_6^{--}$).

The relatively light colour of the salts $KCrOF_4$ and $AgCrOF_4$ apparently precludes the possibility of the presence of chromium in two valency states in these compounds, and indicates that they are derivatives of quinquevalent chromium. The absence of any evidence from *X*-ray data for finite complex ions of the type (MX_5) makes it desirable to produce more evidence before formulating the compounds of empirical formulæ $KCrOF_4$ and $KMnF_5$ with such finite ions. Complexes Tl_2AlF_5 (Brosset, *Z. anorg. Chem.*, 1937, **235**, 139) and Cs_2CoCl_5 (Powell and Wells, *J.*, 1935, 359), for example, contain anion chains of (AlF_6) octahedra, and individual ions Cs^+, $(CoCl_4)^{--}$, and Cl^- respectively. Further discussion of the structures of the new complex fluorides reported here is therefore postponed until additional information is available.

Experimental.

Vanadium Compounds.—Sodium vanadate dissolved quietly in boiling bromine trifluoride. The product obtained by immediate removal of the solvent at 45° *in vacuo* contained a considerable quantity of bromine [Found: wt. equiv. to $NaVO_3$ (= 122), 220; V, 22·0; F, 45·2; Br, 13·2%]. Vanadium was determined by reduction to the quadrivalent state by sulphur dioxide, and titration with permanganate; fluorine was determined by the Willard–Winter method, bromine by precipitation as silver bromide. The residue obtained by heating the first product at 100° approximated in composition to $NaVOF_4$ (Found: equiv., 163; V, 29·8; F, 45·2%; Br, nil. Calc. for $NaVOF_4$: equiv., 166; V, 30·7; F, 45·8%). If, however, the solution of the vanadate in bromine trifluoride was heated under reflux in a long-necked quartz flask for 30 minutes before removal of the solvent at 45°, the composition of the residue approximated to $NaVF_6$ (Found: equiv., 186; V, 28·3; F, 57·0%. Calc. for $NaVF_6$: equiv., 188; V, 27·2; F, 60·7%). Nitrosyl chloride (in excess), vanadium pentoxide, and bromine trifluoride yielded *nitrosonium hexafluorovanadate* when the solution was evaporated at 20° (Found: N, 7·9; V, 26·6; F, 57·8. $NOVF_6$ requires N, 7·2; V, 26·2; F, 58·4%). Nitrosonium hexafluorovanadate is a white solid, rapidly hydrolysed by water and decomposing at 60°. Attempts to obtain silver and nitronium hexafluorovanadates gave products intermediate in composition between the tetrafluorooxyvanadates and the hexafluorovanadates.

Chromium Compounds.—When chromium trioxide, dried at 120°, was treated with bromine trifluoride, 64% (in a second experiment, 57%) of the oxygen was evolved; a little chromium was volatilised, presumably as an oxyfluoride. Evaporation of the solution in the usual way gave a product which retained some bromine even after being heated for four hours at 200° (Found: Cr, 37·5; F, 44·8; Br, 9·3%). On prolonged boiling, bromine trifluoride solutions of the product from chromium trioxide become pasty and then solidified; the residue from one of these was analysed after attaining a constant weight *in vacuo* at 20° (Found: Cr, 23·8; F, 43·5; Br, 27·2%). Both analysed products gave aqueous solutions containing ter- and sexa-valent chromium and hydrofluoric acid. The most satisfactory explanation of these observations, in accord with experiments on oxy-salts, appears to be the formation of a thermally unstable compound between $CrOF_3$ and BrF_3 [the calculated composition for $(BrF_3)(CrOF_4)$ is Cr, 19·7; F, 43·5; Br, 30·3%]. If it is assumed that, in both products, each bromine atom is equivalent to one molecule of combined bromine trifluoride, then the ratios of chromium to (fluorine not present as BrF_3) are 1 : 2·8 (high-temperature product) and 1 : 2·85 (low-temperature product).

The action of bromine trifluoride on chromium trioxide–boric oxide and chromyl chloride–boric oxide mixtures yields boron-free residues; thse results are similar to those obtained with sulphuryl chloride and boric oxide, and show that salts containing CrO_3^{++} and SO_3^{++} ions are not formed.

Potassium dichromate was a convenient starting material for the preparation of a complex oxyfluoride derived from the postulated "acid," $(BrF_3)(CrOF_4)$. This salt evolved 71·5% of its oxygen on treatment with bromine trifluoride. After removal of the solvent *in vacuo* at room temperature, the purple residue, of composition $KCrOF_4{\cdot}0{\cdot}5BrF_3$, was hydrolysed by sodium hydroxide solution. Bromine was determined as silver bromide after reduction with sulphurous acid. A portion of the reduced solution was oxidised to chromate by sodium peroxide, and total chromium was determined iodometrically. Fluorine was determined by decomposition with sodium hydroxide solution and precipitation by calcium fluoride in weakly alkaline carbonate-containing solution; the mixed calcium carbonate–calcium fluoride precipitate was washed free from chromate and then treated in the usual way. The alternative Willard–Winter method gave the same result [Found: wt. equiv. to $\frac{1}{2}K_2Cr_2O_7$ (= 147), 253; Cr, 20·2; Br, 14·3; F, 41·0%. $KCrOF_4{\cdot}0{\cdot}5BrF_3$ requires equiv., 251; Cr, 20·7; Br, 15·9; F, 41·5%]. After being heated *in vacuo* for two hours at 70° the residue had the approximate composition $KCrOF_4{\cdot}0{\cdot}3BrF_3$; at 130—150° elimination of bromine was rapidly completed, and *potassium tetrafluoro-oxychromate*(V) remained as a light purple powder, shown by *X*-ray powder photography to be free from potassium fluoride. After hydrolysis with sodium hydroxide, sexavalent chromium was determined iodometrically; tervalent chromium was precipitated as hydroxide by the potassium cyanate–ammonium chloride method, and, after oxidation to chromate, determined iodometrically. Total chromium and fluorine were determined as above [Found: wt. equiv. to $\frac{1}{2}K_2Cr_2O_7$ (= 147), 185; Cr, 28·1; Cr^{III}, 9·2; Cr^{VI}, 18·2; F, 39·8%. $KCrOF_4$ requires equiv., 183; Cr, 28·4; Cr^{III}, 9·5; Cr^{VI}, 19·0; F, 41·5%]. Bromine trifluoride and an equimolecular mixture of potassium chloride and chromium trioxide gave the same product. Silver dichromate was similarly converted into *silver tetrafluoro-oxychromate*(V), a light purple powder which was instantly hydrolysed by moist air, with the formation of silver chromate [Found: wt. equiv. to $\frac{1}{2}Ag_2Cr_2O_7$ (= 216), 254; Ag, 42·4; Cr, 20·5; Cr^{VI}, 13·9; F, 29·5%. $AgCrOF_4$ requires equiv., 252; Ag, 42·8; Cr, 20·6; Cr^{VI}, 13·9; F, 30·2%]. Attempts to obtain a pure nitrosonium salt were unsuccessful.

Manganese Compounds.—Potassium permanganate reacted vigorously with bromine trifluoride; in three experiments the volume of oxygen evolved was 99, 103, and 100% of the theoretical value. Removal of the solvent *in vacuo* at 20° left pink *potassium pentafluoromanganate*(IV) $KMnF_5$, contaminated to a slight extent with the elements of bromine trifluoride. In several preparations the weight of product equivalent to $KMnO_4$ = 158 varied from 185 to 210. One specimen was analysed by decomposition with sodium carbonate solution, and determination of manganese, fluorine, and bromine as the oxide Mn_3O_4, calcium fluoride, and silver bromide respectively [Found: wt. equiv. to $KMnO_4$ (= 158), 195; Mn, 28·7; F, 46·0; Br, 3·8%. $KMnF_5$ requires equiv., 189; Mn, 29·1; F, 50·2%].

Bromine trifluoride and an equimolecular mixture of potassium permanganate and chloride yielded yellow potassium hexafluoromanganite(IV) (Found: Mn, 21·6; F, 44·0; Br, 1·2. Calc. for K_2MnF_6: Mn, 22·3; F, 46·2%). Its identity was confirmed by comparison of its *X*-ray powder photograph with that of a sample of K_2MnF_6 prepared in the wet way [Bellucci, *Atti R. Accad. Lincei*, 1913, **22**, (ii), 579] by Dr. W. G. Palmer.

Potassium pentafluoromanganite(IV) is, like the hexafluoromanganite, decomposed by cold water

with the precipitation of hydrated manganese dioxide; the salt is stable *in vacuo* at 180°. The action of bromine trifluoride on a 1 : 2 mixture of potassium permanganate and chloride yielded the hexafluoromanganite and the tetrafluorobromite.

In view of this formation of derivatives of quadrivalent manganese, the action of bromine trifluoride on manganous iodate (Emeléus and Woolf, *loc. cit.*) was re-investigated. The iodate dissolved in boiling bromine trifluoride, yielding a clear solution which reacted with dry potassium fluoride (without liberation of bromine), forming successively $KMnF_5$ and K_2MnF_6. This indicated that the solution contained quadrivalent manganese; evaporation of the solution at 20° gave only a red product containing much less bromine than would be required for $(BrF_2)(MnF_5)$. This at 140° lost nearly all its bromine, yielding manganese trifluoride (Found: Mn, 46·5; F, 47·5; Br, 4·0. Calc. for MnF_3: Mn, 49·2; F, 50·8%). The action of heat on the product obtained from bromine trifluoride, manganous iodate, and excess of dinitrogen tetroxide yielded a similar residue.

Grateful acknowledgment is made to Professor H. J. Emeléus, F.R.S., for advice and encouragement, and to the Department of Scientific and Industrial Research for a maintenance grant (to A. A. W.).

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175. *The Enzymic Synthesis and Degradation of Starch. Part XIII. Improved Methods for the Fractionation of Potato Starch.*

By P. N. HOBSON, S. J. PIRT, W. J. WHELAN, and STANLEY PEAT.

Modification and improvement of the published methods for the preparation of the two starch components, amylose and amylopectin, are described. Amylose is prepared by a combination of the methods using aluminium hydroxide and thymol (*J.*, 1949, 1; 1948, 1687), and amylopectin by further fractionation with methanol of amylopectin prepared by the thymol method. Properties of typical preparations of these components are described.

THE methods which have been used for the fractionation of starch have been critically reviewed by Schoch (*Adv. Carbohydrate Chem.*, 1945, **1**, 259) and by Kerr ("Chemistry and Industry of Starch," Academic Press, New York, 2nd Edn., 1950, pp. 179—244). Amongst the earliest successful methods was that of electrophoresis devised by Samec and Haerdtl (*Kolloid-Beih.*, 1920, **12**, 281) which was, however, limited in its applicability. Aqueous leaching of starch grains at temperatures of 70° and upwards has also been used as a preparative method and for the subfractionation of starch components (see Kerr, *loc. cit.*). The most widely used method is precipitation of the amylose component as an insoluble complex with alcohols or other substances, amylopectin remaining in solution. The amylopectin is isolated, after removal of the amylose, by precipitation with excess of ethyl or methyl alcohol. Thus, Schoch used butanol and later "Pentasol" (*loc. cit.*), and Bourne, Donnison, Haworth, and Peat (*J.*, 1948, 1687) used thymol and *cyclo*hexanol as amylose precipitants. Whistler and Hilbert (*J. Amer. Chem. Soc.*, 1945, **67**, 1161) employed nitroparaffins, esters, and thiols as precipitants. Later Bourne, Donnison, Peat, and Whelan (*J.*, 1949, 1) reported an alternative method of fractionation in which the amylopectin component was precipitated as an insoluble complex with aluminium hydroxide. This method yields amylose fractions which are consistently less contaminated with branched polysaccharide than are those prepared by the published thymol method.

It may be helpful to other workers in this field if we put on record an account of the modified procedures we have devised for the fractionation of starch and which we have used with good results for more than a year. The percentage overall yields by these methods are low (for amylose 40% of theory, for amylopectin, 8%) but compare favourably with those given by other and more tedious methods designed to yield components of comparable purity.

The modified method for the preparation of amylose is a combination of the aluminium hydroxide and the thymol method (*loc. cit.*). The complex of aluminium hydroxide and amylopectin is first precipitated by mixing aluminium nitrate and aqueous ammonia in the presence of the dispersed starch. It is important to ensure that an excess of ammonia is not added. Failure to observe this precaution causes the amylose finally isolated from the supernatant liquid to be contaminated with amylopectin. It may be that the hydroxide–amylopectin complex is somewhat soluble in an excess of ammonia, although the formation of aluminate ion is slight even in the highest concentrations of ammonia. After "ageing" at 30° for 3 days the mixture is centrifuged and the supernatant amylose solution dialysed to remove salts, which otherwise remain associated with the polysaccharide when it is precipitated with alcohol. Thymol is then added and the amylose complex separates, the precipitation

being complete in 48 hours. Thymol is removed from the complex when the precipitate is washed with ethanol. Both the thymol complex and the thymol-free amylose isolated by this method are crystalline and form rosettes such as are depicted by Kerr (*loc. cit.*) who first reported the isolation of crystalline potato amylose. When examined under polarised light both the thymol complex and the amylose exhibited weak birefringence. The consistent yields of amylose of high blue value are illustrated by the data of Table I where the properties of six successive batches of amylose prepared by this method are listed. The average carbohydrate content (measured by acid hydrolysis) is 98·4% and the average ash content is 0·86%. That the amylose specimens are of a high purity with respect to freedom from amylopectin-like substances may be shown from a consideration of the action of β-amylase on them.

Peat and his co-workers (*Nature*, 1949, **164**, 499; *Biochem. J.*, 1950, **47**, xl) have shown that potato and other amyloses appear to contain branch linkages, as shown by the failure of crystalline sweet potato and purified soya-bean β-amylases to achieve complete conversion of amylose into maltose (see Table I).

TABLE I.

Properties of amyloses prepared by the aluminium hydroxide–thymol method.

					Action of β-amylase.			
					Stock soya.		Purified soya.	
No.	Blue value.	Ash content (%).	Conversion into glucose by acid (%).	Yield (g.).	% Conv.	A.V.	% Conv.	A.V.
1	1·47	0·51	99·4	9·4	96·8	0·056	67·5	0·411
2	1·47	1·84	98·5	8·2	95·5	0·061	—	—
3	1·46	0·98	97·1	8·6	91·5	0·097	—	—
4	1·45	0·46	98·2	9·6	95·9	0·069	70·8	0·381
5	1·49	0·56	99·3	7·3	92·0	0·058	67·5	0·369
6	1·46	0·78	99·0	9·9	96·0	0·045	68·1	0·371

% Conv. = % conversion into maltose; A.V. = absorption value (680 mμ.) of iodine-stained residual polysaccharide; Stock soya = soya-bean preparation containing β-amylase and Z-enzyme; Purified soya = soya-bean β-amylase preparation free from Z-enzyme. Values are based on dry weight of polysaccharide.

Complete conversion of amylose by β-amylase is only approached in the presence of another enzyme, Z-enzyme, which hydrolyses the branch linkages. The stock soya-bean preparation contains both enzymes and the conversion of the potato amyloses by this preparation is only 4% (average) below the percentage conversion into glucose by acid hydrolysis (Table I). If the failure to achieve complete β-amylolysis were due to the presence of amylopectin, only half of which is converted into maltose by β-amylase, it would be necessary to assume that the amylose preparations still contained about 8% of amylopectin. This explanation cannot, however, account for the intensity of the iodine stain of the polysaccharide remaining after hydrolysis by the stock β-amylase preparation. The final average A.V. (680 mμ.) is 0·064. Eight per cent. of amylopectin, giving rise to 4% of limit β-dextrin, of known blue value (0·160), would contribute only 0·006 to this final A.V. It seems more likely that a small amount of the amylose is removed, by spontaneous precipitation (retrogradation), from the sphere of action of the β-amylase, thus causing an apparent lower degree of conversion into maltose. When such retrogradation occurs, the precipitated but finely dispersed amylose exhibits almost the same intensity of iodine stain as it does in solution. The final A.V. (680 mμ.) would in this case be 4% of the original blue value, or 0·058, which is in good agreement with the average value determined experimentally.

The method for the preparation of amylose-free amylopectin consists in the further fractionation of the crude amylopectin prepared by the thymol method (*J.*, 1948, 1687) by the addition (to its aqueous solution) of methanol to a concentration of 17% (by volume). At this concentration the whole of the amylose impurity is precipitated together with some amylopectin. After removal of the precipitate the polysaccharide remaining in solution is precipitated by the addition of excess of methanol. The addition of sodium chloride is necessary to cause coagulation of the polysaccharide. The temperature of precipitation is critical. At 20° the first addition of methanol brings about no precipitation although at 0° the whole of the polysaccharide is precipitated and no fractionation is achieved. The most suitable temperature for fractionation was found to be 15°. Properties of an unfractionated amylopectin and of two purified amylopectins obtained from it are listed in Table II.

Solutions of the methanol-fractionated amylopectins are water-clear, whereas solutions of thymol-amylopectins are opalescent. Other changes taking place in the physical properties of amylopectin preparations on subfractionation with methanol are consistent with the view

that the process is one of removal of a linear, amylose-type component and not merely a separation, according to molecular size, of amylopectins of similar degrees of branching. If the subfractionation were of the latter character it would be conditioned only by molecular weight, whereas it is actually found that the blue values and the degrees of hydrolysis by stock and purified β-amylases of methanol-fractionated amylopectins are lower than the corresponding values for the unfractionated material (Table II). Such changes are to be expected if it is amylose which is being removed by the treatment with methanol.

TABLE II.

Properties of amylopectins prepared by the thymol–methanol method.

Method of fraction.	Blue value.	Ash content (%).	Conversion into glucose by acid (%).	Yield (%).*	Action of β-amylase. Stock soya. % Conv.	Stock soya. A.V.	Purified soya. % Conv.	Purified soya. A.V.
Thymol	0·221	0·73	94·0	—	54·1	0·090	53·1	0·108
Thymol–MeOH	0·165	0·20	98·0	7·1	51·7	0·084	51·4	0·088
Thymol–MeOH	0·170	2·23	98·4	8·4	—	—	—	—

* As % of original thymol–amylopectin. For the explanation of other abbreviations see Table I.

EXPERIMENTAL.

Analytical Methods.—(*a*) For the methods used in determination of (i) iodine stains of polysaccharides, see Bourne, Haworth, Macey, and Peat (*J.*, 1948, 924), (ii) reducing sugar, starch polysaccharides by acid hydrolysis, and ash content, see Pirt and Whelan (*J. Sci. Food Agric.*, 1951, in the press), and (iii) β-amylase activity, see Part X (*J.*, 1950, 3566).

(*b*) *β-Amylolysis of starch polysaccharides.* Stock soya-bean β-amylase which was prepared as in Part II (*J.*, 1945, 882) contains Z-enzyme. Purified soya-bean β-amylase, which was prepared by a method to be published in a later paper of this series, was free from Z-enzyme. The dried polysaccharide (*ca.* 15 mg.), contained in a 25-c.c. flask, was wetted with alcohol and dissolved in 0·012N-sodium hydroxide (10 c.c.) by intermittent heating on a boiling water-bath and neutralised to phenolphthalein with N-sulphuric acid. Acetate buffer (0·2M.; 3 c.c.; pH 4·8) was added, followed by the stock or purified β-amylase solution (equivalent to 800 units of activity), and the whole was diluted to 25 c.c. The digest was incubated at 35° together with a control digest, not containing polysaccharide, which was used for measurements of the reducing power of the enzyme solution. Measurements of reducing sugar, as maltose, were made after 3 and 5 hours, on 5-c.c. portions of the digests. Measurements of A.V. (680 mμ.) were also made by the standard method, referred to above, with a volume of digest equivalent to 1 mg. of original polysaccharide. The conversion limit was always reached within 3 hours.

Preparation of Amylose by Treatment of Starch with Aluminium Hydroxide and Thymol.—(a) *Precipitation of the aluminium hydroxide complex.* Potato starch (100 g.; dry wt.) was creamed with water (500 c.c.) and added, during 15 minutes, to boiling 0·1% sodium chloride solution (3·5 l.), contained in a 5-l. bolt-head flask, with vigorous stirring. Boiling and stirring were continued for a further 45 minutes, whereafter the paste was cooled rapidly in running water to 30°. Aluminium nitrate [$Al(NO_3)_3,9H_2O$; 48·25 g.] dissolved in the minimum quantity of water was stirred into the paste, and ammonia solution (*d* 0·88) was added slowly from a burette, with mechanical stirring, until the mixture was just alkaline to phenolphthalein. The flask was stoppered and the solution allowed to "age" for 3 days at 30° before the aluminium hydroxide complex was removed on the centrifuge (2500 r.p.m. for 30 minutes). The supernatant liquid, usually *ca.* 900 c.c., was dialysed against running tap water for 2 days.

(b) *Precipitation of thymol complex and isolation of amylose.* If precipitation occurred during dialysis the solution was centrifuged and the supernatant liquid acidified by the addition of a few drops of N-sulphuric acid (alkalinity was due to the tap water). Finely powdered thymol (0·132 g./100 c.c. of solution) was added with shaking, and the vessel stoppered and kept at 30° for 48 hours. The amylose–thymol complex was sedimented on the centrifuge and washed twice by shaking it with thymol-saturated water, centrifuging between each washing. Thymol was removed by grinding the precipitate twice with absolute ethanol and washing it twice with ethanol and then ether. Ether and moisture were removed by storage in a vacuum over phosphoric oxide at room temperature, the sample being subsequently stored in a closed bottle.

Fractionation of Thymol-amylopectin with Methanol.—Thymol-amylopectin was prepared by the method of Bourne, Donnison, Haworth, and Peat (*J.*, 1948, 1687). The amylopectin (*ca.* 7·4 g., dry wt.) was moistened with ethanol and partly dispersed in water (800 c.c.) by being heated to boiling with vigorous stirring and boiled for 1 minute. The hot dispersion was autoclaved at 20 lb. pressure for 1 hour and then cooled to 15°. Sodium chloride (1 g.) was added and the solution diluted to 1 l. Methanol (200 c.c.) was added dropwise with rapid stirring and the precipitate which formed was removed on the centrifuge. To the supernatant liquid was added a further quantity (1 g.) of sodium chloride, followed by absolute ethanol (2 volumes). The precipitate was allowed to coagulate and was removed on the centrifuge. It was dried by washing it with ethanol and ether as in the preparation of amylose above.

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176. *The Ultra-violet Absorption Spectra of Some Benzoic Acids With Electron-repelling Substituents.*

By Carl M. Moser and Arthur I. Kohlenberg.

The ultra-violet absorption spectra of benzoic acids, mono- and 2 : 6-di-substituted with the following substituents, methyl, chloro, bromo, methoxyl, and hydroxyl, have been measured from 2000 A. towards the visible region. The three bands that are generally observed have been designated as the A, B, and C bands. It is found that the frequency of the absorption of A is largely independent of, B is very dependent upon, and C is somewhat dependent upon the nature and position of the substituent group. The spectra are discussed in the light of currently accepted hypotheses concerning absorption in the near ultra-violet region.

Although the ultra-violet absorption spectra of a number of classes of organic molecules have been measured, those of aromatic acids have been measured only in a random fashion. In view of the importance of such acids, it seemed desirable to measure the spectra of a number of substituted benzoic acids in a systematic manner in order to provide a further basis for the elucidation of the relationship of ultra-violet spectra to molecular structure. We therefore report the ultra-violet absorption spectra of numerous benzoic acids, *o*-, *m*-, and *p*-monosubstituted and 2 : 6-disubstituted with the following substituent groups—methyl, chloro, bromo, methoxyl, and hydroxyl. The spectra of some of these acids have been previously determined in a number of solvents, but there are only a few measurements recorded of the spectra of organic molecules in the region near 2000 A.

Table I.

Ultra-violet absorption characteristics of substituted benzoic acids.

Acid.	A Band. $\lambda_{max.}$	A Band. log ε.	B Band. $\lambda_{max.}$	B Band. log ε.	C Band. $\lambda_{max.}$	C Band. log ε.	Method of prepn.
Benzoic	2020	3·90	2280	4·00	2710	2·88	1
					2790	2·74	—
o-Toluic	2050	4·09	2280	3·71	2790	2·86	1
m-Toluic	2050	4·12	2320	3·95	2790	3·01	1
p-Toluic	2040	4·12	2360	4·14	—	—	1
2 : 6-Dimethylbenzoic	2020	4·24	—	—	2700	2·86	2
o-Chlorobenzoic	2020	4·27	~2290 *	3·71	2780	2·88	1
m-Chlorobenzoic	2040	4·31	2300	3·92	2840	2·98	1
p-Chlorobenzoic	2020	4·17	2340	4·18	—	—	1
2 : 6-Dichlorobenzoic	2040	4·43	—	—	2640	2·64	3
	~2160	4·01	—	—	2740	2·70	—
o-Bromobenzoic	2050	4·17	~2240	3·80	2620	2·75	1
					2820	2·88	—
m-Bromobenzoic	2060	4·41	~2250	3·92	2800	2·92	1
p-Bromobenzoic	2050	4·17	2400	4·10	—	—	1
2 : 6-Dibromobenzoic	2050	4·48	—	—	2620	2·97	4
	~2260	4·00	—	—	2720	2·94	—
o-Anisic	2060	4·22	2300	3·79	2910	3·43	1
m-Anisic	2060	4·42	2300	3·83	2930	3·39	1
p-Anisic	2050	4·15	2490	4·14	—	—	1
2 : 6-Dimethoxybenzoic	2050	4·43	—	—	2820	3·27	5
Salicylic	2040	4·36	2360	3·86	3070	3·57	1
m-Hydroxybenzoic	2030	4·36	2360	3·78	3010	3·39	1
p-Hydroxybenzoic	2010	4·18	2510	4·09	—	—	1
γ-Resorcylic	2080	4·21	2500	3·80	2770	3·29	6
	~2180	4·15	—	—	3110	3·54	—

* ~ indicates approximate point of inflection.

(1) Purchased from Eastman Kodak Company, Rochester, New York. (2) Berger and Olivier, *Rec. Trav. chim.*, 1927, **46**, 600. (3) Reich *et al.*, *Bull. Soc. chim.*, 1917, **21**, 222. (4) Olivier, *Rec. Trav. chim.*, 1924, **43**, 872. (5) Mauthner, *J. pr. Chem.*, 1929, **121**, 259. (6) Limaye and Kelkar, *J. Indian Chem. Soc.*, 1935, **12**, 788.

The experimental data are recorded in Figs. 1—5 and Table I. The source of the compounds is indicated in Table I. All samples, either commercially obtained or synthesized, were recrystallized from suitable solvents until a constant melting point was obtained that was in agreement with values in the literature.

FIG. 1.

Ultra-violet absorption spectra of : (1) *benzoic acid ;* (2) o-*chlorobenzoic acid ;* (3) m-*chlorobenzoic acid ;* (4) p-*chlorobenzoic acid ;* (5) 2 : 6-*dichlorobenzoic acid.*

FIG. 2.

Ultra-violet absorption spectra of : (1) *benzoic acid ;* (2) o-*anisic acid ;* (3) m-*anisic acid ;* (4) p-*anisic acid ;* (5) 2 : 6-*dimethoxybenzoic acid.*

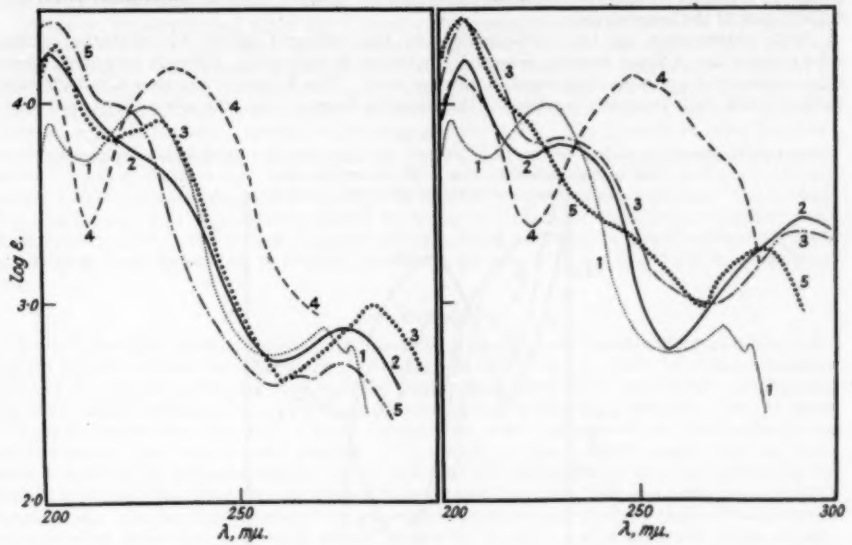
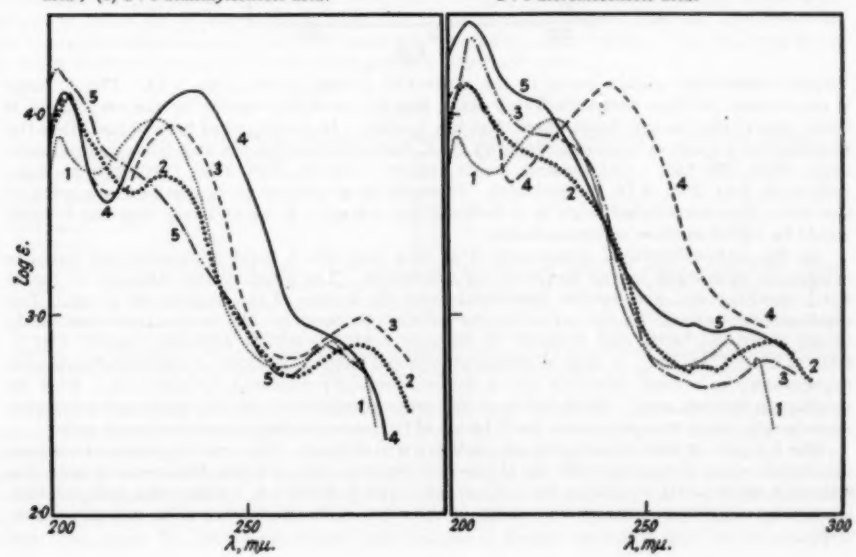


FIG. 3.

Ultra-violet absorption spectra of : (1) *benzoic acid ;* (2) o-*toluic acid ;* (3) m-*toluic acid ;* (4) p-*toluic acid ;* (5) 2 : 6-*dimethylbenzoic acid.*

FIG. 4.

Ultra-violet absorption spectra of : (1) *benzoic acid ;* (2) o-*bromobenzoic acid ;* (3) m-*bromobenzoic acid ;* (4) p-*bromobenzoic acid ;* (5) 2 : 6-*dibromobenzoic acid.*

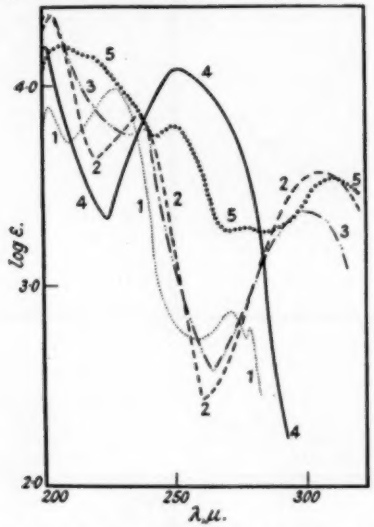


The spectrum of benzoic acid exhibits maxima at the following wave-lengths: 2020, 2280, 2710, and 2790 A. (log ε 3·90, 4·00, 2·88, and 2·74, respectively). The last two maxima in all probability represent vibrational fine structure of one electronic transition. For convenience, the band at 2020 A. will be labelled the A band, that at 2280 A. the B band, and the other two peaks the C band. We now consider the displacements brought about in these bands by further substitution of the benzene ring.

With substitution in the *para*-position to the carboxyl group by electron-repelling substituents, the A band remains essentially constant in frequency, although somewhat more intense than the corresponding band in benzoic acid. The B band undergoes a considerable bathochromic shift from the position of this band in benzoic acid, the amounts of shift with

FIG. 5.

Ultra-violet absorption spectra of: (1) *benzoic acid;* (2) *salicylic acid;* (3) m-*hydroxybenzoic acid;* (4) p-*hydroxybenzoic acid;* (5) *γ-resorcylic acid.*



various substituent groups being in the order OH > OMe > Br > Me > Cl. The C band is not evident in these *para*-substituted acids, but it is probably hidden by the very broad B band rather than having disappeared from the spectra. In a mixture of hexane and ether the spectrum of *p*-hydroxybenzoic acid shows the C band clearly (Castille and Klingstedt, *Compt. rend.*, 1923, **176**, 749). The maxima are as follows: ~2100, 2525, 2750, 2780, 2840 A. (log ε 4·06, 4·18, 3·54, 3·40, 3·18, respectively). It would be of interest to determine the spectra of the other *para*-substituted acids in a hydrocarbon solvent; it seems likely that the C band would be visible in those compounds also.

In the *ortho*-substituted compounds it is seen that the A band of benzoic acid again is essentially unchanged in the frequency of absorption. The position and intensity of the B band, however, are considerably dependent upon the nature of the substituent group. The displacement toward longer wave-lengths of the B band of the *ortho*-substituted acids (when compared with the B band of benzoic acid) is in the following order: OH > OMe > Me ≃ Cl > Br. It is to be particularly noted that the B band of *o*-bromobenzoic acid appears only as a weak inflection and is hypsochromically displaced by about 40 A. from its position in benzoic acid. All B bands of the *ortho*-substituted acids are displaced to shorter wave-lengths when compared with the B bands of the corresponding *para*-substituted acids.

The C bands of the *ortho*-substituted acids are well defined. They are all displaced towards the visible when compared with the C band of benzoic acid, and the displacement is in the following order: OH > OMe > Br > Cl > Me. The C bands of *o*-anisic and salicylic acid are considerably more intense than those of the other *ortho*-substituted acids and of benzoic acid.

The spectra of the *meta*-substituted acids in general show considerable similarity to the spectra of the corresponding *ortho*-substituted acids. The frequency of the A bands remains very close to that of benzoic acid and of the acids substituted in the other positions, but their intensity is greater than that of the latter acids. The B and C bands also occur at nearly the same frequency as in the corresponding *ortho*-acids, although the intensity is usually greater.

In the 2 : 6-disubstituted acids the A band again maintains nearly constant frequency of absorption. In three acids (*viz.*, chloro-, bromo-, and hydroxy-) the band appears to be split so that a reasonably well-defined inflection also occurs to the long wave-length side of the usual position of the A band. In only one acid (γ-resorcylic acid) does the B band appear; the position is shifted to longer wave-lengths when compared with the B band of salicylic acid and is almost equal in frequency to that of *p*-hydroxybenzoic acid. The C bands of three disubstituted acids (methyl-, chloro-, and bromo-) are similar in intensity and frequency of absorption to the C band of benzoic acid. The C band of 2 : 6-dimethoxybenzoic acid is slightly shifted toward longer wave-lengths from its position in benzoic acid and is more intense; the C band of γ-resorcylic acid is considerably shifted to longer wave-lengths than that of benzoic acid (from 2720 to 3110 A.) and is even more intense than the C band of 2 : 6-dimethoxybenzoic acid. In addition, there appears to be a weakly-defined peak near 2770 A. (log ε 3·29) in γ-resorcylic acid.

Discussion.

One of the more generally used hypotheses for a qualitative understanding of ultra-violet spectra might be called the " resonance " theory. Braude *et al.* (*J.*, 1949, 1890) have recently restated the general principles that underlie this approach and have particularly emphasized the relationship between steric inhibition of resonance and electronic spectra. On the basis of these principles the behaviour of the B bands of the *ortho*- and *para*-substituted acids can be rationalized at least with partial success. The structural change that results in going from benzoic acid to the *para*-substituted acids increases the conjugation, and, as elaborated by Braude *et al.* (*loc. cit.*), decreases the energy of excitation, thus resulting in a bathochromic shift of this band. On the basis of resonance considerations alone, the position of the B band in the corresponding *ortho*- and *para*-acids should be nearly the same. The observed hypsochromic shift that has taken place in the spectra of the *ortho*-acids when compared with the B band of the corresponding *para*-acids would be explained on the basis of steric interference to co-planarity between the *ortho*-substituent and the carboxyl group.

Whether the increase of energy of excitation of the *ortho*-acids is primarily due to steric interference can probably be deduced from the following considerations. If the increase in energy of excitation is proportional to the size of the *ortho*-substituent, then the hypothesis of the steric interference to spectra would be at least partially substantiated. This has been done in Table II, with the energy differences translated into cm.$^{-1}$ units.

Table II.

Group.	Increase in energy of excitation (cm.$^{-1}$) of B band in going from *para*- to *ortho*-substituted acid.	Van der Waals radius (A.).[a, b]
Methyl	1487	2·0
Chloro	1125	1·8
Bromo	2193	1·95
Methoxyl	3155	*c*
Hydroxyl	2532	*c*

[a] Values obtained from Pauling, " The Nature of the Chemical Bond," p. 188, Cornell Univ. Press (1940). [b] Braude *et al.* (*loc. cit.*) have suggested that the van der Waals radii are probably too large a measure of the intramolecular interference properties of atoms. Even if this is true, a corrected measure of interference should be proportional to the van der Waals radii. [c] The van der Waals radii for the hydroxyl and the methoxyl group are not given by Pauling. The value given for oxygen is 1·40 A. An inspection of molecular models of salicylic acid and *o*-anisic acid indicates that there is very little interference in the former compound, but that it is considerable in the latter.

It will be observed that there appears to be little direct relationship between the increase in energy and the size of the substituent group. Particularly interesting is the low value for the increase in the energy of excitation observed for the methyl group, even though the size of this group would indicate that the energy of excitation should be very considerable, and the high value for the small hydroxyl group. It may be that the shifts in frequency of the B band should not be assigned alone to steric interference with coplanarity. Klevens and Platt (*J. Amer. Chem. Soc.*, 1949, **71**, 1014) have stated that changes in *location* of bands that are observed in

other derivatives may be partly due to inductive and similar effects of the substituent on the ring, but changes of *intensity* observed in the bands are to be accounted for almost entirely by steric interference to resonance. Although it is generally assumed that the resonance effects of any substituent group in the *ortho*- and *para*-positions are the same, the inductive effects would not be, and they no doubt play a part in the energy of excitation, though the exact amount cannot yet be determined. In such a geometrically small group as the hydroxyl group the difference in inductive effect appears to be rather considerable.

In the 2 : 6-disubstituted acids the steric interference to coplanarity would be expected to be very considerable, and the absence of a B band in all these compounds except γ-resorcylic acid is not surprising. An examination of a molecular model of γ-resorcylic acid indicates that there is only a small amount of steric interference between the carboxyl group and the two *ortho*-hydroxyl groups.

The interpretation of the B bands of the *meta*-substituted acids on this basis is rather more complex. Since there is no resonance interaction between the substituent and the carboxyl group, it might be assumed, as a first approximation, that the effect of the substituents on the displacement of the corresponding band in benzene that occurs near 2035 A. would be nearly additive after allowance for a small hypsochromic shift due to cross-conjugation effects (Branch and Calvin, "The Theory of Organic Chemistry," p. 172, Prentice-Hall, New York, 1940). This assumption was tested upon Doub and Vandenbelt's data (*J. Amer. Chem. Soc.*, 1947, **69**, 2714; 1949, **71**, 2414) for the frequency of the B band in the monosubstituted benzene compounds. The agreement between the calculated and measured values for the frequency of the B bands of the *meta*-substituted acids varied from rather good in the case of *m*-hydroxybenzoic acid to rather poor in that of *m*-anisic acid. It would seem that the simple assumptions made for the calculation are not sufficient accurately to account for the B bands of the *meta*-substituted acids.

It is of interest to observe the close similarity in the frequency of absorption of the B bands of the corresponding *meta*- and *ortho*-substituted acids. This similarity has been observed in the spectra of a large number of *ortho*- and *meta*-disubstituted benzenoid compounds by Doub and Vandenbelt (*loc. cit.*). Their suggestion that stabilization of the photo-excited state might be able to take place across *meta*-positions, even though this is not possible in the ground state, would not appear to account for the position of the B band of *m*-bromobenzoic acid, which is shifted to shorter wave-lengths than that of benzoic acid. It is noteworthy in connection with the B band of *m*-bromobenzoic acid that, although an inspection of the molecular model of this acid indicates that there is no steric interference to coplanarity between the bromine atom and the carboxyl group, nevertheless the band appears only as a reasonably well-defined inflection. It would appear that other factors than steric interference to coplanarity are able to bring about shifts of bands to shorter wave-lengths and to diminish the intensity of absorption. An explanation offered (see below) to account for the similarity of the position of the C bands of corresponding *ortho*- and *meta*-substituted acids may also hold for the similarity of the position of the B bands.

Inspection of the data reveals that the C bands also are very similar in both the corresponding *ortho*- and *meta*-substituted acids. However, it will be seen that steric interference between the carboxyl group and another atom or group apparently has no effect upon this band. For example, the B band is barely visible in the spectrum of *o*-bromobenzoic acid while the C band is as intense as the C band of benzoic acid and has undergone a bathochromic shift of approximately 110 A. from the position of this band in benzoic acid. In 2 : 6-dibromobenzoic acid, where there is considerable steric interference between the bromine atoms and the carboxyl group, the C band is similar in position and intensity to that of benzoic acid.

The similarity in frequency of absorption of the C bands of the corresponding *ortho*- and *meta*-substituted acids has received a quantum-mechanical explanation by Förster (*Z. Naturforsch.*, 1947, **2a**, 149) based on geometrical symmetry considerations. It is possible that a similar explanation would hold for the similarity of the B bands.

Both the bands that have been labelled B and C in this paper have usually been associated with benzenoid absorption. They have been assumed to arise by the displacement of the bands of benzene occurring near 2035 and 2540 A. that has been brought about by substitution of the benzene ring. Qualitatively, these bands have been accounted for on the assumption that light is absorbed along non-identical optical axes, perpendicular to each other (Lewis and Calvin, *Chem. Reviews*, 1939, **25**, 273; Jones, *ibid.*, 1948, **43**, 429; Cram and Cranz, *J. Amer. Chem. Soc.*, 1950, **72**, 595). This conception has received support from Coulson's LCAO calculations (*Proc. Physical Soc.*, 1948, **60**, 257). If this should be a satisfactory explanation for these bands, it is

of considerable interest to ascertain why steric interference to resonance has a marked effect upon the B band but apparently none on the C band.

The A bands in these acids remain, through numerous changes of position and substituent group, reasonably constant in frequency of the maxima although varying rather considerably in intensity. Morton and Stubbs (*J.*, 1940, 1347) suggested that the bands observed by Castille and Klingstedt (*loc. cit.*) near 2060 A. in the monohydroxybenzoic acids are due to the selective absorption of the carboxyl group. It might appear that, since all the acids reported in this paper also show bands in this region, the suggestion has been strengthened. However, the intensity of the band that appears in the region in the spectra of numerous aliphatic acids is of the order of log ε 1·7—2·0 (Ley and Arends, *Z. physikal. Chem.*, 1932, **17**, *B*, 177), while the bands reported in this paper are of the order of log ε 4·0. The intensity of the A band is thus probably too high to be ascribed to the carboxyl group and should probably be ascribed to benzenoid absorption also. In this case the band would be the displacement of the band in benzene that occurs near 1870 A. The splitting of this band that is visible in the spectra of 2 : 6-dichlorobenzoic, 2 : 6-dibromobenzoic, and γ-resorcylic acid is to be ascribed to the absorption of light along perpendicular axes (Platt, *J. Chem. Physics*, 1949, **17**, 484).

In all probability the most consistent explanation of the observed spectra that can now be offered is that the bands are due to the displacement of those of benzene. No simple explanation can yet be advanced as to why the perturbations of the individual bands are so different. Only a quantum-mechanical theory going in detail into the effect of substituent groups on the general potential field of the molecule and electron interactions is likely to provide an analysis of the ultra-violet spectra which will hold for more than a few special cases. Such a study is now in progress.

Experimental.—The spectra were measured with the aid of a Beckman quartz spectrophotometer, Model DU, equipped with a hydrogen lamp obtained from Mr. A. G. Nestor, Lansdowne, Pennsylvania. The spectra were determined in 95% ethanol from 2200 A. towards the visible region. Although it has been reported by Harrison, Lord, and Loofbourow ("Practical Spectroscopy," New York, 1948, p. 418), that carefully purified 95% ethanol (Leighton, Cary, and Schipp, *J. Amer. Chem. Soc.*, 1931, **53**, 3017) yields a solvent sufficiently good for work to 2000 A., we were not able to purify 95% ethanol so that it was sufficiently transparent at shorter wave-lengths than 2150 A. to be suitable as a solvent (a complete description of the attempted purification will be published elsewhere). Therefore, a mixture of 99·5% of distilled water + 0·5% of 95% ethanol (carefully purified) was used as the solvent in the region from 2000 A. to 2200 A. A comparison of our data in alcohol with those for the same compounds in water (Doub and Vandenbelt, *loc. cit.*) indicates that the spectra are essentially the same. In alcohol the peaks are usually shifted by 10—20 A. towards shorter wave-lengths and are slightly less intense.

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177. *Experiments on the Preparation of Indolocarbazoles. Part IV. The Preparation of Indolo(3′ : 2′-1 : 2)carbazole.*

By Muriel L. Tomlinson.

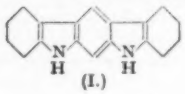
Bis*cyclo*hexanone *m*-phenylenedihydrazone has been made and converted, by treatment with acetic acid, into 5 : 6 : 7 : 8 : 4′ : 5′ : 6′ : 7′-octahydroindolo(3′ : 2′-1 : 2)carbazole which has been dehydrogenated to give indolo(3′ : 2′-1 : 2)carbazole.

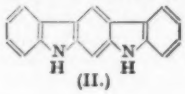
None of the five isomeric indolocarbazoles appears to have been made *, and in previous attempts to prepare them and their simple derivatives (*e.g.*, Manjunath, *J. Indian Chem. Soc.*, 1927, **4**, 271; Bond, Deegan, and Plant, *J.*, 1949, S 160; Coker, Plant, and Turner, *J.*, 1950, 110), the

* *Added in proof.*—I am indebted to Mr. J. D. Bu'Lock for calling my attention to the recent paper by Fearon and Boggust (*Biochem. J.*, 1950, **46**, 62). These authors suggest that urorosein base is indolo(3′ : 2′-2 : 3)carbazole, but the composition they give, $C_{18}H_{10}N_2$, corresponds to a dehydroindolocarbazole.

only success was that of Clifton and Plant (*J.*, 1950, 461) who obtained 6-cyanoindolo(2′ : 3′-3 : 4)carbazole by pyrolysis of 1-3′-carbazolyl-5-cyanobenzotriazole.

Bis*cyclo*hexanone *m*-phenylenedihydrazone (*N*′*N*‴-di*cyclo*hexylidene-*m*-phenylenedihydrazine) has now been made and converted into an octahydroindolocarbazole which has been dehydrogenated to the corresponding indolocarbazole by heating it with palladium–charcoal. This dihydrazone is extremely easily decomposed by acids which immediately colour it red and, of the many different conditions investigated for bringing about a Fischer indole synthesis with it, only two were in any way successful. Its alcoholic solution, containing slightly more than the requisite amount of 2N-aqueous sulphuric acid, deposits ammonium sulphate in considerable


(I.)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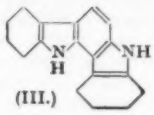
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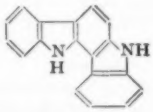
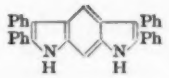
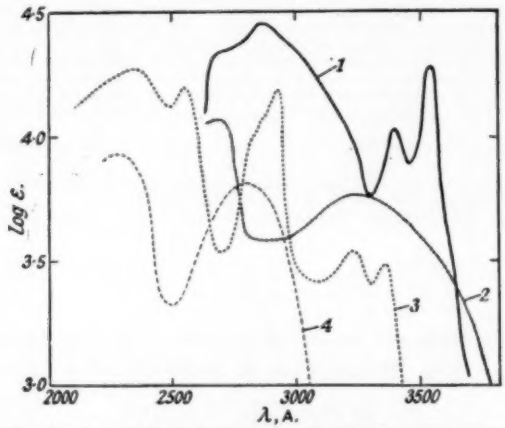



(V.)

quantity after being brought to boiling point and cooled, but only a small amount of the indole can be isolated; a more satisfactory yield is obtained by using acetic acid.

Two structures are possible for indolocarbazoles prepared from *m*-phenylenedihydrazones: investigation has revealed the presence of only one product in the present work, and the octahydro-compound and the indolocarbazole obtained from it must be respectively either (I) and (II), or (III) and (IV). Of these 5 : 6 : 7 : 8 : 4′ : 5′ : 6′ : 7′-octahydroindolo(3′ : 2′-1 : 2)carbazole (III) and indolo(3′ : 2′-1 : 2)carbazole (IV) are preferred, both on theoretical



1. *Indolo*(3′ : 2′-1 : 2)*carbazole*. 2. 5 : 6 : 7 : 8 : 4′ : 5′ : 6′ : 7′-*Octahydroindolo*(3′ : 2′-1 : 2)*carbazole*. (1 *and* 2 *in dioxan solution.*)
3. *Carbazole*. 4. 1 : 2 : 3 : 4-*Tetrahydrocarbazole*. (3 *and* 4 *in methanol solution.*)

grounds and from analogy with such reactions as the Skraup reaction with *m*-phenylenediamine (Smith, *J. Amer. Chem. Soc.*, 1930, **52**, 397). In this connection, however, it should be noted that Ruggli and Petitjean (*Helv. Chim. Acta*, 1936, **19**, 928) prefer the "linear" structure (V) for the compound, m. p. 279°, which they prepared from bisdeoxybenzoin *m*-phenylenedihydrazone and identified as the substance, m. p. 282°, obtained by Japp and Meldrum (*J.*, 1899, **75**, 1044) from *m*-phenylenediamine and benzoin. They base their preference on analogy with the compound that Japp and Meldrum (*loc. cit.*, p. 1039) made from resorcinol and benzoin and from which Dischendorfer (*Monatsh.*, 1933, **62**, 263) has obtained 4 : 6-dibenzoylresorcinol by oxidation and hydrolysis.

The identity of the substances prepared by Japp and Meldrum and by Ruggli and Petitjean has been confirmed: the product of each reaction has now been obtained, by sublimation in hydrogen, as colourless plates, m. p. 287°, which show a violet fluorescence, intense in ultra-violet light and visible even in daylight, but the structure of this compound is not considered to have been finally settled.

The ultra-violet absorption spectra of indolo(3′ : 2′-1 : 2)carbazole and its octahydro-compound have been determined (in dioxan solution because a solution of the latter in alcohol darkens) and these are shown in the figure, in comparison with the ultra-violet absorption spectra of carbazole and 1 : 2 : 3 : 4-tetrahydrocarbazole.

In the light of experience with bis*cyclo*hexanone *m*-phenylenedihydrazone further attempts have been made to convert bis*cyclo*hexanone *p*-phenylenedihydrazone (Clifton and Plant, *loc. cit.*) into an octahydroindolocarbazole. The observations of the original workers have been confirmed and these attempts were also unsuccessful. The compound decomposed with brisk effervescence in cold glacial acetic acid, and, although application of the above alcohol–sulphuric acid method to this substance yielded ammonium sulphate, the desired octahydroindolo-carbazole was not obtained. The hydrazone has been treated with very dilute acetic and sulphuric acids under a variety of conditions. The product was generally a brown amorphous powder that did not crystallise from any of the common solvents and gave considerable quantities of carbazole, but no indolocarbazole, on dehydrogenation.

Experimental.

*Bis*cyclo*hexanone* m-*Phenylenedihydrazone.*—*cyclo*Hexanone (6·0 c.c.) was dissolved in a solution of *m*-phenylenedihydrazine hydrochloride (Schoutissen, *Rec. Trav. chim.*, 1935, **54**, 253) (4·3 g.) in water (300 c.c.), and the mixture was treated gradually, with thorough shaking, with crystalline sodium acetate (6·0 g.). The *dihydrazone* thus obtained was recrystallised from alcohol and it separated as orange-yellow prisms, m. p. 155° (2·5 g.) (Found: C, 72·9; H, 9·2; N, 18·4. $C_{18}H_{26}N_4$ requires C, 72·5; H, 8·7; N, 18·8%). It decomposes to a black resinous mass when kept and some decomposition seems to occur on recrystallisation.

5 : 6 : 7 : 8 : 4′ : 5′ : 6′ : 7′-*Octahydroindolo*(3′ : 2′-1 : 2)*carbazole.*—The above dihydrazone (1·0 g.) was mixed with glacial acetic acid (5 c.c.) and the deep-red solution so formed was carefully warmed over a steam-bath for a few minutes until it became brown. It was then set aside for 24 hours, whereupon a crystalline solid separated from the dark brown solution. This was collected and washed, first with acetic acid and then with water (yield, 0·4 g.). Recrystallisation from glacial acetic acid afforded 5 : 6 : 7 : 8 : 4′ : 5′ : 6′ : 7′-*octahydroindolo*(3′ : 2′-1 : 2)*carbazole* as pale grey prisms, m. p. 228° (Found: C, 81·7; H, 7·9; N, 10·5. $C_{18}H_{20}N_2$ requires C, 81·8; H, 7·6; N, 10·6%). It is insoluble in dilute acids, and in concentrated sulphuric acid it forms a colourless solution, not coloured by addition of nitric acid. In benzene solution it shows a weak grey-blue fluorescence in ultra-violet light, and its solutions in alcohol and benzene darken fairly rapidly.

Indolo(3′ : 2′-1 : 2)*carbazole.*—The above octahydro-compound was mixed with about half its volume of palladium–charcoal and gradually heated in an atmosphere of hydrogen. After being kept at 240° for 20 minutes the temperature was slowly raised to 320° and heating was continued for a further 30 minutes. *Indolo*(3′ : 2′-1 : 2)*carbazole* sublimed as colourless plates, m. p. 299—300° (Found: C, 84·5; H, 4·8. $C_{18}H_{12}N_2$ requires C, 84·4; H, 4·7%). Extraction of the catalyst with acetic acid or benzene afforded more indolocarbazole, m. p. 295°, which was purified by sublimation in hydrogen. The yield was nearly theoretical. In concentrated sulphuric acid this substance forms a yellow solution that is changed, by nitric acid, to a deep green, fading to red-brown; nitric acid alone converts it into a green solid. In the solid state, and in benzene solution, it shows a brilliant violet fluorescence in ultra-violet light. It was recovered essentially unchanged after being boiled with acetic anhydride for 5 hours.

Dehydrogenation of the dried amorphous solid, obtained by adding water to the dark brown solution from which the octahydro-compound first separated, afforded a small quantity (about 0·1 g.) of indolo-(3′ : 2′-1 : 2)carbazole, m. p. 295°, raised to 298° by admixture with the above. Resublimation in hydrogen gave the pure indolocarbazole, m. p. 299—300°.

The author expresses her thanks to Dr. S. G. P. Plant for his interest and for his suggestion that this investigation, begun some time ago, should be pursued.

The Dyson Perrins Laboratory, Oxford University. [*Received, November 22nd,* 1950.]

178. *The Retardation of Benzaldehyde Autoxidation by* p-*Cresol.*

By William A. Waters and Charles Wickham-Jones.

A kinetic study has been made of the effect of *p*-cresol on the benzoyl peroxide-catalysed autoxidation of benzaldehyde. The decomposition of perbenzoic acid by a first-order acid–base-catalysed process tends to complicate the reaction kinetics of the early stages of the autoxidation. This effect can be controlled by the initial addition of sufficient benzoic acid. In these circumstances, the rate of autoxidation is (*a*) approximately proportional to the square root of the benzoyl peroxide concentration, (*b*) proportional to the square of the benzaldehyde concentration, (*c*) inversely proportional to the *p*-cresol concentration, and (*d*) nearly independent of the oxygen concentration. These results can be accounted for by postulating that *p*-cresol acts in the main as a chain transfer agent, and that chain termination involves the destruction of *p*-tolyl radicals principally by dimersation.

This paper deals with a kinetic approach to the general problem of the mode of action of monohydric phenols in retarding, or inhibiting, the autoxidation of organic liquids. *p*-Cresol has been selected for this study because a considerable amount of information concerning the way in which it undergoes oxidation when treated with free-radical producing agents has recently been accumulated in this laboratory (Cosgrove and Waters, *J.*, 1949, 3189). Benzaldehyde was chosen as the autoxidisable substrate chiefly because it absorbs oxygen so easily at moderate temperatures to give almost exclusively the known products, benzoic acid and perbenzoic acid. However, it now appears that aldehydes are by no means ideal substrates for autoxidation studies, since the oxidation process as a whole is seriously complicated by the ease of decomposition of the initially-formed per-acids. Fortunately, with perbenzoic acid, this decomposition is in the main an acid–base-catalysed process (cf. Wittig and Pieper, *Annalen*, **1941**, **546**, 142) which can be controlled by adding a sufficient amount of benzoic acid initially to the reacting system (see p. 816).

The initiation of the autoxidation of all reasonably well-purified organic substances is probably to be ascribed to residual traces of catalytically active impurities in the substance itself or on the walls of the reaction vessel. Consequently, the autoxidation of " purified " benzaldehyde is a rather erratic process at the outset, some workers even claiming that highly purified benzaldehyde does not autoxidise (see Bailey, " The Retardation of Chemical Reactions," Arnold, London, 1937, Chap. 11). Our own early measurements showed large rate variations from run to run, but they became much more reproducible when the decomposition of the perbenzoic acid was controlled as mentioned above. Eventually we obtained consistent results by this means and by also swamping the action of the adventitious catalysts by adding known amounts of benzoyl peroxide so as to provide a regular source of active free benzoate radicals for initiating autoxidation chains, and thereafter we were able to elucidate the modes of action of *p*-cresol as a retarding agent. The outcome of this work is considered in the following sections.

(I) *The Role of Perbenzoic Acid.*

It was established by Bäckström (*J. Amer. Chem. Soc.*, 1927, **49**, 1460) that the uptake of oxygen by benzaldehyde is essentially a chain reaction, whose propagation steps we may now represent by equations (1) and (2). This cycle yields perbenzoic acid as the initial reaction product, but

(1) $$Ph\text{-}\overset{\overset{O}{\|}}{C}\cdot + O_2 \longrightarrow Ph\text{-}\overset{\overset{O}{\|}}{C}\text{-}O\text{-}O\cdot$$

(2) $$Ph\text{-}\overset{\overset{O}{\|}}{C}\text{-}O\text{-}O\cdot + Ph\text{-}\overset{\overset{O}{\|}}{C}\text{-}H \longrightarrow Ph\text{-}\overset{\overset{O}{\|}}{C}\text{-}O\text{-}O\text{-}H + Ph\text{-}\overset{\overset{O}{\|}}{C}\cdot$$

the latter soon breaks down so that, when the autoxidation of benzaldehyde has proceeded for some time, benzoic acid accumulates at a rate almost identical with that of oxygen uptake (Almquist and Branch, *J. Amer. Chem. Soc.*, 1932, **54**, 2293) and thereafter the reaction apparently becomes simple as in equation (3).

(3) $$2Ph\cdot CHO + O_2 \longrightarrow 2Ph\cdot CO_2H$$

In the absence of added catalysts, or inhibitors, the rapid autoxidation of benzaldehdyde does appear to slacken according to the second-order relationship

$$-\mathrm{d}[\tfrac{1}{2}\mathrm{O}_2]/\mathrm{d}t = -\mathrm{d}[\mathrm{Ph{\cdot}CHO}]/\mathrm{d}t = k\,.\,[\mathrm{Ph{\cdot}CHO}]^2$$

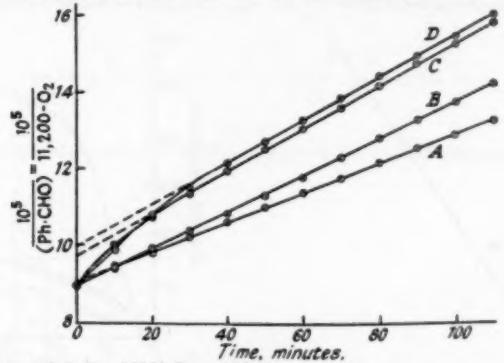
since Fig. 1, in which Δ[Ph·CHO] has been computed in terms of the total oxygen uptake, shows that the integrated expression for a second-order reaction

$$1/[\mathrm{Ph{\cdot}CHO}] = kt + \text{constant}$$

does hold for quite a considerable time interval both for benzaldehyde alone and for mixtures with the inert diluent chlorobenzene.

FIG. 1

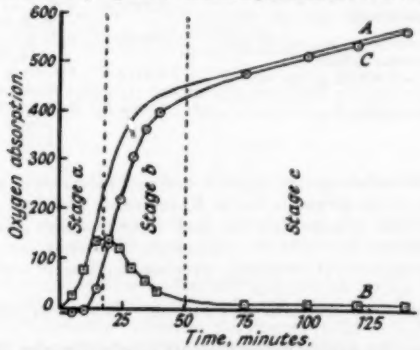
Oxidation of benzaldehyde–chlorobenzene mixtures at 20·0°.



Curves A & B : 100% *Benzaldehyde.*
Curve C : 50% *Benzaldehyde* + 50% *chlorobenzene.*
Curve D : 20% *Benzaldehyde* + 80% *chlorobenzene.*
[$\mathrm{O_2}$ = *oxygen absorbed (in ml. at N.T.P. per mole of benzaldehyde).*]

FIG. 2.

Oxidation of a p-cresol–benzaldehyde mixture at 30·0°.



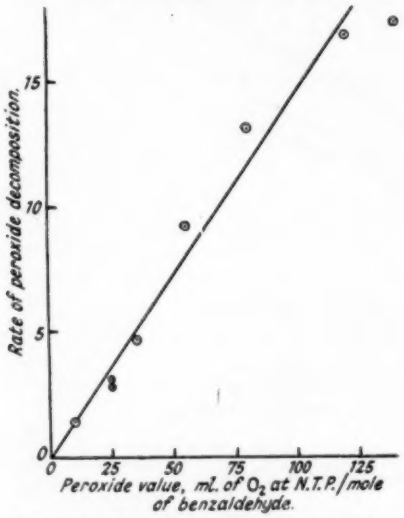
Concentration of p-cresol = 0·00053 *g./10 ml. of benzaldehyde.*
Curve A : Oxygen absorption (ml. of $\mathrm{O_2}$ *at N.T.P./mole of benzaldehyde).*
Curve B : Peroxide values
Curve C : Peroxide decomposition values } *calculated as equivalents of the oxygen absorbed.*

In the chosen circumstances, the initial phase of the autoxidation occurred too rapidly for investigation. Fig. 2, however, which gives a typical autoxidation curve for benzaldehyde containing a very small amount of *p*-cresol, shows that the reaction includes both an initial,

brief, autocatalytic stage *a* in which the rate of oxygen uptake (see curve *A*) increases with time, and a subsequent stage *b* of autoxidation at diminishing rate, which is finally succeeded by a prolonged stage *c* of slowish but almost constant rate of reaction. The titratable peroxide content of the liquid (see curve *B*) rises in stage *a* to a maximum, approximately coincident with the moment of fastest oxygen uptake, and then falls off during stage *b* to a low but steady value, which remains almost constant in stage *c*. It may be noted that the rate of peroxide decomposition, which may be plotted from the measurements of (oxygen uptake) − (peroxide value) (see curve *C*), increases with time, and, at identical peroxide concentrations, is very much faster after the peroxide has attained its peak value (stage *b*) than before it (stage *a*).

FIG. 3.

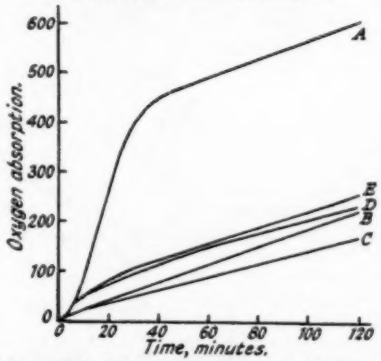
Decomposition of peroxide during the oxidation of a p-cresol–benzaldehyde mixture at 30·0°.



Rate of peroxide decomposition in ml. of O_2 *(at N.T.P.)/min./mole of benzaldehyde.*
Concentration of p-cresol = 0·00053 g./10 ml. of benzaldehyde.
Results calculated from data of Fig. 2.

FIG. 4.

Effect of acids and bases on the oxidation of a p-cresol–benzaldehyde mixture at 30·0°.



Oxygen absorption in ml. of oxygen (at N.T.P.)/mole of benzaldehyde.
Concentration of p-cresol = 0·00106 g./10 ml. of benzaldehyde.
Initial addition of acid or base (to 10 ml. of benzaldehyde):

Curve A: none.
Curve B: 0·55 g. of benzoic acid (0·0455 mole/mole benzaldehyde).
Curve C: 0·21 g. of trichloroacetic acid (0·013 mole/mole benzaldehyde).
Curve D: 0·5 ml. of pyridine (0·0625 mole/mole benzaldehyde).
Curve E: 0·48 g. of anhydrous potassium carbonate (0·035 mole/mole benzaldehyde).

Fig. 3, obtained by correlating the slope of curve *C* in stages *b* and *c* of Fig. 2 with the corresponding peroxide value given in curve *B*, indicates that the rate of perbenzoic acid decomposition is a first-order process once the peak value has been passed. This substantiates Wittig and Pieper's findings (*loc. cit.*) for benzaldehyde–carbon tetrachloride mixtures and accords with the simple equation (4) originally proposed by Baeyer and Villiger (*Ber.*, 1900, **33**, 1569).

$$(4) \quad Ph{\cdot}CO{\cdot}O{\cdot}O{\cdot}H + Ph{\cdot}CHO \longrightarrow 2Ph{\cdot}CO_2H$$

Almquist and Branch (*loc. cit.*) were the first workers to discover that the peroxide content of autoxidising benzaldehyde passed through a peak value. They showed that this peak was not exhibited by samples of benzaldehyde to which benzoic acid had been added initially, and that the peroxide content of such mixtures quickly rose to a steady value. Their interpretation of this phenomenon involved the postulation of the existence of both active and inactive forms of the peroxide. Wittig and Pieper have, more correctly, ascribed the effect of benzoic acid upon the rate of decomposition of perbenzoic acid to acid catalysis of the Baeyer and Villiger reaction (4). They suggested that the benzoic acid catalyses an acetal-like addition of perbenzoic

acid to benzaldehyde to yield a complex (I) which rapidly breaks down into two benzoic acid molecules :

$$Ph{\cdot}CO_3H + Ph{\cdot}CHO \longrightarrow Ph{-}\underset{\underset{O}{\|}}{C}{-}O{-}O{-}\overset{\overset{H}{|}}{\underset{\underset{OH}{|}}{C}}{\cdot}Ph \longrightarrow 2Ph{\cdot}CO_3H$$

(I.)

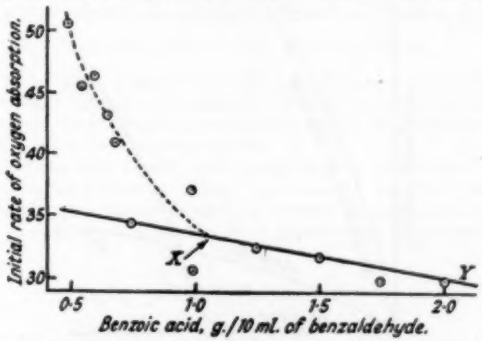
We have confirmed this work, and in addition have shown that other acids, *e.g.*, trichloroacetic acid, and bases, *e.g.*, pyridine and anhydrous potassium carbonate, have a similar effect (see Fig. 4). We therefore suggest that the formation of the benzaldehyde–perbenzoic acid complex (I) is an acid–base-catalysed reaction, typical of a carbonyl addition process, and proceeds thus :

acids :
$$Ph{-}\underset{\underset{O}{\|}}{C}H + H{-}A + \overset{\overset{H}{|}}{O}{-}O{-}CO{-}Ph \longrightarrow Ph{-}\underset{\underset{OH}{|}}{\overset{\overset{+H^+}{|}}{C}}H{-}O{-}O{-}CO{-}Ph + A^- \longrightarrow (I)$$

bases :
$$Ph{-}\underset{\underset{O}{\|}}{C}H + \overset{\overset{H + A^-}{|}}{O}{-}O{-}CO{-}Ph \longrightarrow Ph{-}\underset{\underset{O^-}{|}}{\overset{\overset{+H{-}A}{|}}{C}}H{-}O{-}O{-}CO{-}Ph \longrightarrow (I)$$

FIG. 5.

Initial oxygen absorption rates at 40·0° at different benzoic acid concentrations.



Rate in ml. of oxygen (at N.T.P.) per min. per mole of benzaldehyde.
$[Bz_2O_2]$ = 0·2000 *g./10 ml. of benzaldehyde.*
$[p\text{-}C_6H_4Me{\cdot}OH]$ = 0·000424 *g./10 ml. of benzaldehyde.*

The decomposition of the complex (I) can follow the ionic scheme suggested by Robertson and Waters (*J.*, 1948, 1574) for the reaction of Caro's acid with ketones :

$$Ph{-}\overset{\overset{OH}{|}}{C}{-}O{-}O{-}CO{-}Ph \longrightarrow Ph{-}\overset{\overset{OH}{|}}{\overset{+}{C}}{-}O{-}H + {}^-O{-}CO{-}Ph \longrightarrow 2Ph{\cdot}CO_3H$$

(I.)

This involves the migration of hydrogen as an anionoid group from carbon to an adjoining oxygen atom so as to effect the oxidation of the benzaldehyde moiety.

This acid–base-catalysed reaction between perbenzoic acid and benzaldehyde cannot, however, be the only type of decomposition which perbenzoic acid can undergo, for, in all stages of the autoxidation, changes in the oxygen-uptake rate are associated with changes in the peroxide content of the aldehyde (see Fig. 2), just as is found in the autoxidation of tetralin (Robertson and Waters, *J.*, 1948, 1585), ethyl linoleate (Bolland and Gee, *Trans. Faraday Soc.*, 1946, **42**, 236), and similar substances. In these latter cases, the acceleration of the autoxidation rates has been ascribed to the production of additional chain-starting radicals by the homolytic peroxide decomposition (5).

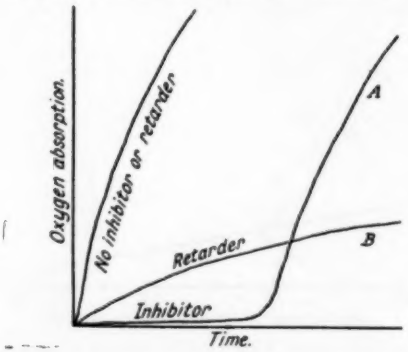
$$(5) \quad R{-}O{-}O{-}H \longrightarrow R{-}O{\cdot} + {\cdot}O{-}H$$

The ionic reactions of perbenzoic acid described above would not produce fragments capable of initiating fresh autoxidation chains. We would therefore suggest that some slight homolytic decomposition also occurs to give small traces of $Ph{\cdot}CO_2{\cdot}$ and ·OH radicals, both of which would be autoxidation chain initiators. In this way the form of curve *A* in Fig. 2 can be qualitatively accounted for, since a reaction of type (5) would occur increasingly as the peroxide content of the reaction mixture rises (stage *a*), but will become very slight again as the peroxide content decreases (stage *b*) owing to the onset of the acid-catalysed decomposition.

If we add a sufficient quantity of acid or base initially to the benzaldehyde–*p*-cresol system, we can cut out stages *a* and *b* of Fig. 2 and proceed at once with the steady state of stage *c* (see Fig. 4). Fig. 5 shows the effect of benzoic acid on the initial rate of oxygen uptake for a mixture containing both *p*-cresol and benzoyl peroxide. At a benzoic acid concentration corresponding to point *X*, the equilibrium concentration of perbenzoic acid is rapidly reached; further addition of benzoic acid serves only to dilute the reacting liquid, and the subsequent decrease in the initial oxygen-uptake rate is approximately the same as that which would be achieved by adding a corresponding molar fraction of an inert diluent (the slope of the line *XY* in Fig. 5 is that calculated for the addition to the mixture of an inert diluent of molecular weight 122). In the kinetic investigations (Section II), we have always added initially a greater

FIG. 6.

Typical effects of inhibitors and retarders on autoxidation systems.



amount of benzoic acid than is indicated by point *X* in Fig. 5 (in the majority of cases, this was 1·50 g./10 ml. of benzaldehyde; in the remainder, the amount varied and the experimental value of the oxygen-uptake rate was corrected for this variation).

(II) *The Kinetics of the Retarded Autoxidation.*

The significant feature of the autoxidation of benzaldehyde in the presence of *p*-cresol is the fact that oxygen uptake proceeds at a slow but yet steady rate for a long time. Even when the oxidising liquid has taken up several hundred moles of oxygen per mole of *p*-cresol, the rate-controlling action of the latter is still operative. Hence *p*-cresol must act in a different way from those inhibitors of autoxidation which are slowly consumed during an " induction period " of very slow oxidation, and thereafter exert no decided check on the reaction velocity—*e.g.*, many unsaturated hydrocarbons (Wittig and Pieper, *Annalen*, 1947, **558**, 207) and anthracene (Branch, Almquist, and Goldsworthy, *J. Amer. Chem. Soc.*, 1933, **55**, 4052). These inhibitors give an autoxidation curve of type *A* (see Fig. 6) and their destruction during the induction period has in certain instances been demonstrated by physical and chemical tests (Wittig and Pieper, *loc. cit.*, 1947; Bäckström and Beatty, *J. Physical Chem.*, 1931, **35**, 2530; Alyea and Bäckström, *J. Amer. Chem. Soc.*, 1929, **51**, 90). The much greater persistence of a retarder such as *p*-cresol, however (which gives an autoxidation curve of type *B* in Fig. 6), may be inferred from the very long time in which it operates (as compared with the action of inhibitors of the former type). Indeed, the slow autoxidation of *n*-butaldehyde containing a little *p*-cresol has been carried out until over 90% of the aldehyde has been oxidised to butyric acid, and yet in the

resulting product over 60% of the *p*-cresol has been found still to be present (private communication from Dr. D. G. Jones, Imperial Chemical Industries Limited, Billingham).

It therefore follows that in an autoxidation process of the usual chain type

Initiation : $\text{Catalyst} + \text{RH} \longrightarrow \text{R}\cdot$

Propagation : $\begin{cases} \text{R}\cdot + \text{O}_2 \longrightarrow \text{RO}_2\cdot \\ \text{RO}_2\cdot + \text{RH} \longrightarrow \text{RO}_2\text{H} + \text{R}\cdot \end{cases}$

Termination : $2\text{RO}_2\cdot \text{ (or R}\cdot\text{)} \longrightarrow \text{inert products}$

the role of *p*-cresol cannot be only the removal of active radicals (R·, RO_2·, etc.) or of catalyst, as is the case for inhibitors giving curves of type *A* (Fig. 6), but must also be that of a retarding agent which hinders the main oxidation chain by chemical reactions in which it is re-formed. Such a role is possible only with a *chain transfer agent* which substitutes a sequence of slow reactions for a sequence of rapid ones.

The chemical properties of phenols are such as to permit them to act as chain transfer agents in reactions involving homolytic dehydrogenation, since the removal of a hydrogen atom from a monohydric phenol (Aryl–O–H) yields a mesomeric semi-quinol radical (Aryl–O·) which is much more stable than a free alkyl or aryl radical, but much less stable than the semi-quinone radical ion ($^-\!:\!O\text{–}C_6H_4\text{–}O\cdot$) of a 1 : 2- or 1 : 4-dihydric phenol. Consequently, one can reasonably postulate that the semi-quinol radical of a monohydric phenol may be capable of dehydrogenating easily autoxidisable substrates thus (cf. Cosgrove and Waters, *J.*, in the press) :

$$\text{Aryl–O}\cdot + \text{RH} \longrightarrow \text{R}\cdot + \text{Aryl–O–H}$$

Bolland and ten Have (*Disc. Faraday Soc.*, **1947**, **2**, 252) have tentatively suggested that this may be possible, but could adduce no evidence for it from their own work. Bickel and Waters (*J.*, 1950, 1764), however, have already found some experimental evidence of a similar process in reactions associated with vinyl polymerisation.

Normally the (Aryl-O·) radicals will tend to accumulate, and, as the study of their organic chemistry has shown in this laboratory, they can eventually combine with each other to form complex phenol dimers; again we have found no evidence of their reaction with free oxygen.

Thus a retarded autoxidation involving chain transfer can be represented by the following reaction sequence :

Chain initiation : $\begin{cases} \text{Bz}_2\text{O}_2 \xrightarrow{k_1} 2\ \text{Ph}\cdot\text{CO}_2\cdot & \ldots\ (1) \\ \text{Ph}\cdot\text{CO}_2\cdot + \text{RH} \xrightarrow{k_2} \text{Ph}\cdot\text{CO}_2\text{H} + \text{R}\cdot & \ldots\ (2) \end{cases}$

Chain propagation : $\begin{cases} \text{R}\cdot + \text{O}_2 \xrightarrow{k_3} \text{RO}_2\cdot & \ldots\ (3) \\ \text{RO}_2\cdot + \text{RH} \xrightarrow{k_4} \text{RO}_2\text{H} + \text{R}\cdot & \ldots\ (4) \end{cases}$

Chain transfer : $\begin{cases} \text{R}\cdot + \text{ArOH} \xrightarrow{k_5} \text{RH} + \text{ArO}\cdot & \ldots\ (5) \\ \text{RO}_2\cdot + \text{ArOH} \xrightarrow{k_6} \text{RO}_2\text{H} + \text{ArO}\cdot & \ldots\ (6) \\ \text{ArO}\cdot + \text{RH} \xrightarrow{k_7} \text{ArOH} + \text{R}\cdot & \ldots\ (7) \end{cases}$

Chain termination : $\begin{cases} 2\text{ArO}\cdot \xrightarrow{k_8} \text{phenol dimer} & \ldots\ (8) \\ \text{and similar reactions} \end{cases}$

where Bz_2O_2 denotes chain-initiating catalyst (benzoyl peroxide), RH denotes substrate (benzaldehyde), and ArOH denotes retarder (*p*-cresol).

By taking reactions (1)—(8) only, and by considering the stationary states (i) $d[\text{Ph}\cdot\text{CO}_2\cdot]/dt = 0$, (ii) $d[\text{ArO}\cdot]/dt = 0$, (iii) $d[\text{R}\cdot]/dt = 0$, and (iv) $d[\text{RO}_2\cdot]/dt = 0$, we have the equations

(i) $\frac{1}{2}k_1[\text{Bz}_2\text{O}_2] = k_2[\text{RH}][\text{Ph}\cdot\text{CO}_2\cdot]$

(ii) $k_5[\text{Ar}\cdot\text{OH}][\text{R}\cdot] + k_6[\text{Ar}\cdot\text{OH}][\text{RO}_2\cdot] = k_7[\text{RH}][\text{ArO}\cdot] + k_8[\text{ArO}\cdot]^2$

(iii) $k_2[\text{RH}][\text{Ph}\cdot\text{CO}_2\cdot] + k_4[\text{RH}][\text{RO}_2\cdot] + k_7[\text{RH}][\text{ArO}\cdot] = k_3[\text{O}_2][\text{R}\cdot] + k_5[\text{Ar}\cdot\text{OH}][\text{R}\cdot]$

(iv) $k_3[\text{O}_2][\text{R}\cdot] = k_4[\text{RH}][\text{RO}_2\cdot] + k_6[\text{Ar}\cdot\text{OH}][\text{RO}_2\cdot]$

Adding (i), (ii), (iii), and (iv), we have

$$\tfrac{1}{2}k_1[Bz_2O_2] = k_3[ArO\cdot]^2$$

so that

$$[ArO\cdot] = \{k_1[Bz_2O_2]/2k_3\}^{\frac{1}{2}}$$

From (ii)

$$[RO_2\cdot] = \frac{k_7[RH][ArO\cdot] + k_3[ArO\cdot]^2 - k_5[Ar\cdot OH][R\cdot]}{k_6[Ar\cdot OH]}$$

Substituting this in (iv), we have

$$k_2[O_2][R\cdot]k_6[Ar\cdot OH] = \{k_4[RH] + k_6[Ar\cdot OH]\}\{k_7[RH][ArO\cdot] + k_3[ArO\cdot]^2 - k_5[Ar\cdot OH][R\cdot]\}$$

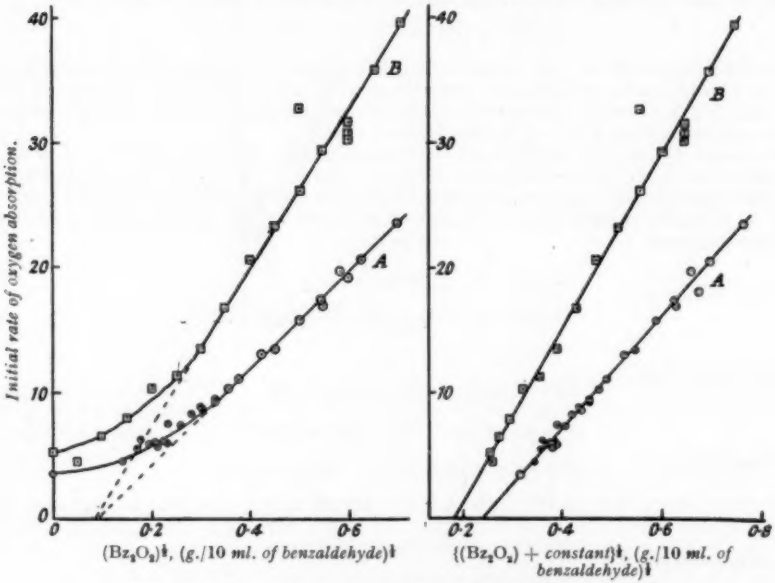
whence

$$-d[O_2]/dt = k_2[O_2][R\cdot]$$

$$= \frac{k_2[O_2]\left\{k_4[RH] + k_6[Ar\cdot OH]\right\}\left\{k_7[RH]\left(\frac{k_1}{2k_3}[Bz_2O_2]\right)^{\frac{1}{2}} + \frac{k_1}{2}[Bz_2O_2]\right\}}{[Ar\cdot OH]\{k_2k_6[O_2] + k_4k_5[RH] + k_5k_6[Ar\cdot OH]\}}$$

FIG. 7. FIG. 8.

Initial oxygen absorption rates at 40·0° at different benzoyl peroxide concentrations.



Rates of absorption in ml. of oxygen (at N.T.P.)/min./mole benzaldehyde.
Curve A : [*p*-C_6H_4Me·OH] = 0·00106 *g./10 ml. of benzaldehyde.*
Rates corrected to [Ph·CO_3H] = 1·50 *g./10 ml. of benzaldehyde.*
Curve B : [*p*-C_6H_4Me·OH] = 0·000636 *g./10 ml. of benzaldehyde.*
[Ph·CO_3H] = 1·50 *g./10 ml. of benzaldehyde.*

An examination of the reaction sequence (1)—(8) suggests that at small retarder concentrations: (*a*) Reaction (4) will probably be much faster than reaction (6) since [RH] ≫ [Ar·OH]; hence, as an approximation we can put $k_4[RH] \gg k_6[Ar\cdot OH]$. (*b*) Reaction (7) may well be much faster than reaction (8) since [RH] ≫ [ArO·], and one knows that the homolytic dehydrogenation of aldehydes is a very easy process. If this is so, we can make the approximation $k_7[RH] \gg k_3[ArO\cdot] = \{\tfrac{1}{2}k_1k_3[Bz_2O_2]\}^{\frac{1}{2}}$.

With these two approximations, we obtain the kinetic relationship (A)

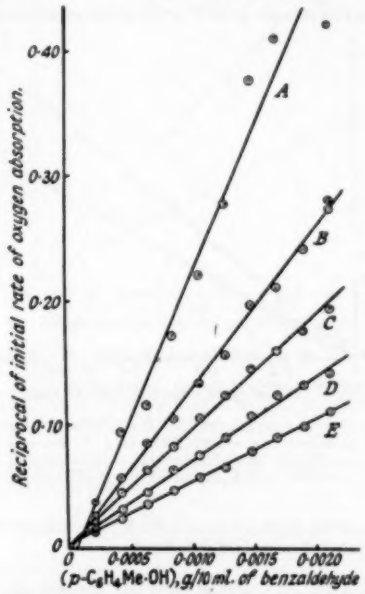
$$-\mathrm{d}[O_2]/\mathrm{d}t = \frac{k_3k_4k_7[O_2][RH]^{\frac{3}{2}}\left\{\frac{k_1}{2k_8}[Bz_2O_2]\right\}^{\frac{1}{2}}}{[Ar{\cdot}OH]\{k_3k_6[O_2] + k_4k_5[RH]\}} \quad . \quad . \quad . \quad . \quad . \quad (A)$$

which is in better accord with our experimental findings than the equations which can be deduced from alternative postulates (see Table, p. 822).

Fig. 7 shows that the rate of autoxidation of a benzaldehyde–*p*-cresol mixture is approximately proportional to the half power of the benzoyl peroxide concentration at large values of the latter only, but the extrapolation of this linear plot does not pass through the origin. At zero benzoyl peroxide concentration, there is still an appreciable oxidation rate, so benzoyl peroxide is not the only chain-initiating catalyst present in the system.

FIG. 9.

Initial oxygen absorption rates at 40·0° at different p-cresol concentrations.



Rates of absorption in ml. of oxygen (at N.T.P.)/min./mole of benzaldehyde.
Benzoyl peroxide concentrations (g./10 ml. of benzaldehyde) : Curve A, 0·0200; Curve B, 0·0543 Curve C, 0·1086; Curve D, 0·2000; Curve E, 0·3000.
Rates corrected to [Ph·CO_3H] = 1·50 *g./10 ml. of benzaldehyde in each case except curve D where no correction was necessary.*

These features of Fig. 7 may be satisfactorily accounted for by suggesting : (i) an additional chain initiation

$$X \xrightarrow{k_1'} X\cdot$$

followed by

$$X\cdot + RH \xrightarrow{k_2'} XH + R\cdot$$

where X possibly represents that fraction of the decomposition of perbenzoic acid which is chain starting (see Section I, p. 815); (ii) an additional unimolecular chain-termination reaction (9) as well as the bimolecular reaction (8). It is difficult to picture the organic chemistry of such a radical destruction as reaction (9), unless it is perhaps a surface reaction.

$$ArO\cdot \xrightarrow{k_9} \text{inert products} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

The postulation of these additional reactions will modify the term $\{k_1[Bz_2O_2]/2k_3\}^{\frac{1}{2}}$ in equation (A) to the more complex form

$$\sqrt{\frac{k_1}{2k_3}}\sqrt{[Bz_2O_2] + \frac{2k_1'}{k_1}[X] + \frac{k_2^2}{2k_1k_3}} - \frac{k_2}{\sqrt{2k_1k_3}}$$

whilst the terms involving [RH], $[O_2]$, and [Ar·OH] are unaltered.

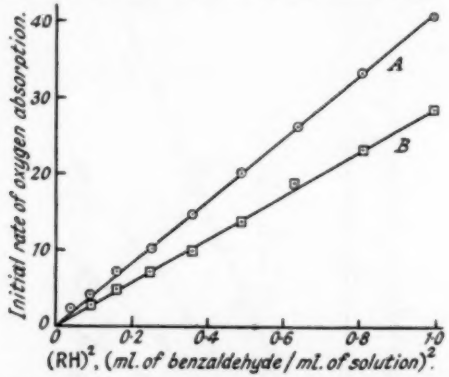
From the experimental data of Fig. 7, it is possible to derive, by the method of successive approximations, a linear relation of the form

$$d[O_2]/dt = a\{\sqrt{[Bz_2O_2] + b} - c\}$$

for *all* concentrations of $[Bz_2O_2]$, which is shown in Fig. 8. Constant a, measured by the slope of the plot, of course depends on the concentrations of the other components in the system, but

FIG. 10.

Initial oxygen absorption rates at 40·0° at different benzaldehyde concentrations.



Rates of absorption in ml. of oxygen (at N.T.P.)/min./mole of benzaldehyde. Chlorobenzene used as diluent. Concentrations in g./10 ml. of solution.
Curve A: $[Bz_2O_2] = 0{\cdot}3000$; $[p\text{-}C_6H_4Me\text{·}OH] = 0{\cdot}000424$; $[Ph\text{·}CO_3H] = 1{\cdot}78$.
Curve B: $[Bz_2O_2] = 0{\cdot}3000$; $[p\text{-}C_6H_4Me\text{·}OH] = 0{\cdot}000636$; $[Ph\text{·}CO_3H] = 1{\cdot}50$.

b and c should, from the modified form of equation (A), be independent constants indicative of the additional reactions postulated in (i) and (ii) above.

Fig. 9 shows that

$$1/\{-d[O_2]/dt\} \propto [Ar\text{·}OH] + \text{constant}$$

where the constant, which clearly is indicative of the extent of chain termination not involving *p*-cresol, is so small that its nature can be ignored in our work.

Again, the experimental results plotted in Fig. 10 (obtained with benzaldehyde–chlorobenzene mixtures) show that the rate of oxidation is proportional to the second power of the benzaldehyde concentration, and Fig. 11 shows that it is dependent on the oxygen concentration in the following way:

$$[O_2]/\{-d[O_2]/dt\} = p[O_2] + q$$

i.e.,

$$-d[O_2]/dt = [O_2]/\{p[O_2] + q\}$$

Ignoring that part of this relation which is independent of *p*-cresol (which, we have already shown, is very small), we find that, at atmospheric pressure, q is much smaller than $p[O_2]$; for this reason, we have been unable to determine its kinetic dependence on other variables—any deviation from the experimental result, $-d[O_2]dt \propto [RH]^2$, caused by this small term q would not show in Fig. 10.

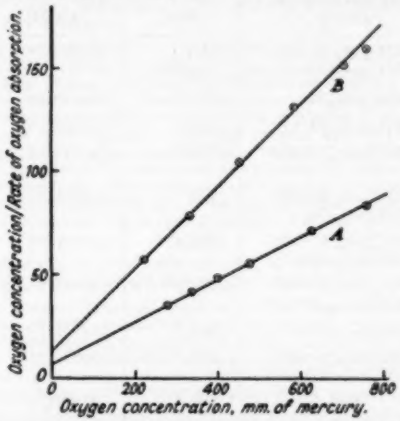
Thus our experimental results substantiate our view that reactions (1)—(4) and (6)—(9) are the important ones occurring during the autoxidation of a benzaldehyde–*p*-cresol system. There

is in addition, however, a very small denominator term which could perhaps be accounted for by the introduction of reaction (5). In this connection we would point out that we can expect the ratio k_3/k_4 to be very large (cf. Bamford and Dewar, *Proc. Roy. Soc.*, **1949**, **198**, *A*, 252), which would lead to the condition $k_3k_5[O_2] \gg k_4k_5[RH]$.

Although we have successfully compared our experimental results with the modified form of the kinetic equation (A) derived from the reactions (1)—(9), it is of interest to compare them also with alternative hypotheses. The natures of the radical-catalysed chain initiation and chain propagation processes are so well established by other workers on autoxidation that we need only

FIG. 11.

Initial oxygen absorption rates at 40·0° at different oxygen concentrations.



Oxygen concentrations in mm. of Hg; *rates of absorption in ml. (at N.T.P.)/min./mole of benzaldehyde. Concentrations in g./10 ml. of solution.*
Curve A : $[Bz_2O_2] = 0{\cdot}3000$; $[p\text{-}C_6H_4Me\cdot OH] = 0{\cdot}00212$; $[Ph\cdot CO_3H] = 1{\cdot}54$. (10 *Ml. of* Ph·CHO.)
Curve B : Chlorobenzene used as diluent. $[Bz_2O_2] = 0{\cdot}3000$; $[p\text{-}C_6H_4Me\cdot OH] = 0{\cdot}00106$; $[Ph\cdot CO_3H] = 1{\cdot}50$. (5 *Ml. of* Ph·CHO + 5 *ml. of* PhCl.)

consider alternative chain termination reactions (which must, of course, involve *p*-cresol). Of these, the most plausible are given below :

$$ArO\cdot + R\cdot \xrightarrow{k_{10}} \text{inert products} \quad (10)$$

$$ArO\cdot + RO_2\cdot \xrightarrow{k_{11}} \text{,, ,,} \quad (11)$$

$$ArO\cdot + RO_2\cdot \xrightarrow{k_{11a}} \text{,, ,,} + O_2 \quad (11a)$$

$$ArO\cdot + PhCO_3\cdot \xrightarrow{k_{12}} \text{,, ,,} \quad (12)$$

$$Ar\cdot OH + R\cdot \xrightarrow{k_{13}} \text{,, ,,} \quad (13)$$

$$Ar\cdot OH + RO_2\cdot \xrightarrow{k_{14}} \text{,, ,,} \quad (14)$$

$$Ar\cdot OH + RO_2\cdot \xrightarrow{k_{14a}} \text{,, ,,} + O_2 \quad (14a)$$

In the Table, a summary of the kinetic equations derived by introducing each of these termination reactions, with and without chain transfer, is given. It is seen that our results cannot be explained by any likely reaction sequence other than that marked *, which we have discussed in detail above.

It is interesting to note that reaction (12), which has in fact been found to occur by Cosgrove and Waters (*loc. cit.*, 1949), must be negligible in this autoxidation system. We suggest that this can be accounted for by the rapidity of reaction (2) involving the substrate, which in effect

prevents any appreciable number of $Ph{\cdot}CO_2{\cdot}$ radicals from reacting with the few $ArO{\cdot}$ radicals present in the mixture.

Reaction (14) has been postulated by Bolland and ten Have (*Trans. Faraday Soc.*, 1947, **43**, 201) for the inhibition of the autoxidation of ethyl linoleate by quinol. It is significant that it leads to different kinetics for the autoxidation process from those found by ourselves. This may well be due to the different degrees of reactivity of semi-quinol radicals ($Aryl{-}O{\cdot}$) and semi-quinone radicals ($^{-}{:}O{-}C_6H_4{-}O{\cdot}$), and also to the difference in the ease of dehydrogenation of the two autoxidising liquids.

Chain-transfer reactions.	Chain-termination reactions.	Approximations (if any).	Proportionality of $-d[O_2]/dt$ to: [RH].	[ArOH].	$[O_2]$.	$[Bz_2O_2]$.
* (5), (6), & (7)	(8) & (9)	$k_4[RH] \gg k_6[Ar{\cdot}OH]$ $k_7[RH] \gg k_9[ArO{\cdot}] + k_9$	$\frac{[RH]^2}{\alpha+\beta[RH]}$	$[Ar{\cdot}OH]^{-1}$	$\frac{[O_2]}{\alpha[O_2]+\beta}$	$\{[Bz_2O_2]+\alpha\}^{\frac{1}{2}}-\beta$
(5) & (7)	(10)	$k_7[RH] \gg k_{10}[R{\cdot}]$	$[RH]^{\frac{1}{2}}$	$[Ar{\cdot}OH]^{-\frac{1}{2}}$	$[O_2]$	$[Bz_2O_2]^{\frac{1}{2}}$
(5) & (7)	(11)	$k_7[RH] \gg k_{11}[RO_2{\cdot}]$	$[RH]$	$[Ar{\cdot}OH]^{-\frac{1}{2}}$	$[O_2]^{\frac{1}{2}}$	$[Bz_2O_2]^{\frac{1}{2}}$
(5) & (7)	(11*a*)	$k_7[RH] \gg k_{11a}[RO_2{\cdot}]$	$\alpha[RH]-\beta$	$\alpha[Ar{\cdot}OH]^{-\frac{1}{2}}-\beta$	$\alpha[O_2]^{\frac{1}{2}}-\beta$	$\alpha[Bz_2O_2]^{\frac{1}{2}}-\beta[Bz_2O_2]$
(6) & (7)	(10)	$k_4[RH] \gg k_6[Ar{\cdot}OH]$ $k_7[RH] \gg k_{10}[R{\cdot}]$	$[RH]$	$[Ar{\cdot}OH]^{-\frac{1}{2}}$	$[O_2]^{\frac{1}{2}}$	$[Bz_2O_2]^{\frac{1}{2}}$
(6) & (7)	(11)	$k_4[RH] \gg k_6[Ar{\cdot}OH]$ $k_7[RH] \gg k_{11}[RO_2{\cdot}]$	$[RH]^{3/2}$	$[Ar{\cdot}OH]^{-\frac{1}{2}}$	$[O_2]^{0}$	$[Bz_2O_2]^{\frac{1}{2}}$
(6) & (7)	(11*a*)	$k_4[RH] \gg k_6[Ar{\cdot}OH]$ $k_7[RH] \gg k_{11a}[RO_2{\cdot}]$	$\alpha[RH]^{3/2}-\beta$	$\alpha[Ar{\cdot}OH]^{\frac{1}{2}}-\beta$	$[O_2]^{0}$	$\alpha[Bz_2O_2]^{\frac{1}{2}}-\beta[Bz_2O_2]$
(5) & (7)	(12)	$k_7[RH] \gg k_{12}[Ph{\cdot}CO_2{\cdot}]$	$[RH]^2$	$[Ar{\cdot}OH]^{-1}$	$[O_2]$	$[Bz_2O_2]^{0}$
(6) & (7)	(12)	$k_4[RH] \gg k_6[Ar{\cdot}OH]$ $k_7[RH] \gg k_{12}[Ph{\cdot}CO_2{\cdot}]$	$[RH]^2$	$[Ar{\cdot}OH]^{-1}$	$[O_2]^{0}$	$[Bz_2O_2]^{0}$
none	(5), (10), & (11)	none	$[RH]^{0}$	$[Ar{\cdot}OH]^{-1}$	$[O_2]$	$[Bz_2O_2]$
none	(5) & (11*a*)	none	$[RH]^{0}$	$\alpha[Ar{\cdot}OH]^{-1}-\beta$	$\alpha[O_2]-\beta$	$[Bz_2O_2]$
none	(6) & (10)	none	$\alpha[RH]+\beta$	$\alpha[Ar{\cdot}OH]^{-1}+\beta$	$[O_2]^{0}$	$[Bz_2O_2]$
none	(6) & (11)	none	$\alpha[RH]+\beta$	$\alpha[Ar{\cdot}OH]^{-1}+\beta$	$[O_2]^{0}$	$[Bz_2O_2]$
none	(6) & (11*a*)	none	$\alpha[RH]+\beta$	$\alpha[Ar{\cdot}OH]^{-1}+\beta$	$[O_2]^{0}$	$[Bz_2O_2]$
none	(13)	none	$[RH]^{0}$	$[Ar{\cdot}OH]^{-1}$	$[O_2]$	$[Bz_2O_2]$
none	(14)	none	$\alpha[RH]+\beta$	$\alpha[Ar{\cdot}OH]^{-1}+\beta$	$[O_2]^{0}$	$[Bz_2O_2]$
none	(14*a*)	none	$[RH]$	$[Ar{\cdot}OH]^{-1}$	$[O_2]^{0}$	$[Bz_2O_2]$

Experimental.

Purification of Materials.—Benzaldehyde (B.P.C.) was kept over anhydrous potassium carbonate before being fractionally distilled under a reduced pressure of nitrogen into a blackened flask possessing a side-arm inlet tube with tap, through which nitrogen was passed whenever a sample of the benzaldehyde was subsequently pipetted out for use. Cylinder nitrogen was purified for this purpose by a train consisting of (*a*) two bottles of Fieser's solution (40 g. of potassium hydroxide, 8 g. of sodium anthraquinone-β-sulphonate, and 30 g. of sodium dithionite in 200 ml. of water; Fieser, *J. Amer. Chem. Soc.*, 1924, **46**, 2639), (*b*) a bottle of saturated lead acetate solution, (*c*) a bottle of concentrated sulphuric acid, (*d*) a tower of potassium hydroxide pellets, and (*e*) a mercury "blow-off." The benzaldehyde purified in this way was shown by analysis to contain less than 0·15% of benzoic acid and less than 0·015% of peroxide.

p-Cresol was distilled under reduced pressure, and subsequently stored in a vacuum-desiccator over concentrated sulphuric acid. A standard solution of the compound in benzaldehyde was prepared whenever necessary by transferring a small glass cup containing an accurately weighed sample of *p*-cresol to a 500-ml. blackened flask possessing a side-arm inlet tube with tap. Purified nitrogen was passed through this flask whilst a known volume of benzaldehyde was transferred from the storage vessel by means of a pipette. The resulting solution was kept under nitrogen throughout.

Benzoyl peroxide was recrystallised from hot chloroform, and stored in a vacuum-desiccator over concentrated sulphuric acid; it had m. p. 101—102° (Found: peroxide content >98%). Benzoic acid and trichloroacetic acid were recrystallised and stored in a vacuum-desiccator over concentrated sulphuric acid. Chlorobenzene and pyridine were dried and fractionated before use.

Measurement of Oxygen Absorption.—The apparatus consisted essentially of a reaction vessel (a Pyrex-glass bulb of approx. diameter 4 cm., fitted with a neck *ca.* 18 cm. long and 1·4 cm. in diameter) connected by means of B.14 joints and flexible rubber pressure tubing to a glass manometric system. The latter consisted of a butyl phthalate manometer, a graduated gas burette of 50-ml. capacity containing mercury and provided with a levelling tube, and gas leads for the admission of dry oxygen and for evacuation of the system when required. Each portion of the apparatus could be controlled by a tap. The reaction vessel was placed in a closely-fitting black cloth bag to prevent light from entering the reaction mixture, and was shaken horizontally by an electrical shaker at a rate of about 900 cycles/min. with an amplitude of *ca.* 0·4 cm.; under these conditions the rate of oxygen diffusion through the liquid was greater than the rate of oxygen absorption, since duplicate pieces of apparatus operating at different shaking speeds gave concordant oxygen-uptake rates. The reaction vessel was immersed in a water-thermostat controlled to $\pm 0{\cdot}05°$.

The reaction vessel and pipettes were very carefully cleaned before each run with methanolic sodium hydroxide, followed by concentrated nitric acid. They were then rinsed well with distilled water and ethyl alcohol, and dried in the steam-oven.

For each run the procedure was as follows: A known amount of benzoic acid was weighed into the reaction vessel (placed in position as described above). A small, carefully cleaned glass cup, containing an accurately weighed sample of benzoyl peroxide, was introduced, followed by known volumes of the stock benzaldehyde and *p*-cresol solutions, discharged from pipettes to give a total volume of 10 ml. The reaction vessel was then quickly closed, and the whole system evacuated at the water pump for 1 minute without shaking and ½ minute with shaking. Cylinder oxygen, after traversing a mercury lute, a wash-bottle containing concentrated sulphuric acid, and a tower of phosphoric oxide, was introduced into the system, after which the gas burette was read at atmospheric pressure and the shaking recommenced. Subsequent burette readings were made at room temperature and atmospheric pressure at suitable time intervals, and were computed as ml. of oxygen at N.T.P./mole of benzaldehyde. It was necessary to make a slight correction for the oxygen physically dissolved in the liquid at the commencement of each run.

In the absence of benzaldehyde, a chloroform solution of equimolecular amounts of *p*-cresol and benzoyl peroxide showed no tendency to absorb oxygen when heated at 30°.

Determination of Peroxide Values.—The results given in Fig. 2 were obtained by measuring both the oxygen absorption and the peroxide values of a single reaction mixture (30 ml.). The former were obtained by the method described in the preceding section, shaking being stopped at suitable time intervals to allow a 1-ml. sample to be extracted with a pipette; the reaction vessel and manometric system were re-evacuated and refilled with oxygen before shaking was recommenced, the stop-clock timing the reaction being stopped and started simultaneously with the shaking.

Peroxide values were determined iodometrically by the technique used by Robertson and Waters (*J.*, 1948, 1578) for the determination of tetralin hydroperoxide, in which iodine liberation was completed at 80° under a carbon dioxide atmosphere.

Determination of the Reaction Kinetics.—The experimental data of two operators (Mrs. A. M. B. and C. W. J.), using similar but independent sets of apparatus, have been combined in Figs. 7 *A*, 8 *A*, 9 *A*, *B*, *C*, and *E*, and 10 *A*. No distinction between the two is apparent.

Initial rate of reaction. This was computed as the average rate of oxygen absorption over the first 10·5 minutes, from the oxygen uptake figures at 1, 10, and 11 minutes. This proved to be more satisfactory than the noting of the time required for the absorption of a pre-determined volume of oxygen, since it was found to eliminate irregularities associated with the commencement of the reaction.

Change in benzaldehyde concentration. The results for this were obtained by diluting the benzaldehyde with chlorobenzene. Chlorobenzene is admirable for this purpose, since it will be comparatively inert towards the reacting mixture, and its molar concentration per unit *volume* is approximately the same as that of benzaldehyde; hence the molar concentrations of the reactants will be unaltered in Fig. 10 where the total initial volume of benzaldehyde and chlorobenzene remains constant.

Change in oxygen concentration. This was effected by connecting the "free" open side of the butyl phthalate manometer to a closed volume (carefully tested for leaks), whose pressure could be reduced to any constant value, read on a mercury manometer. Oxygen absorption measurements were then made at this known reduced pressure in the usual manner.

We thank Mrs. A. M. Bishop for assistance with the experimental work. This work has been carried out at the request of the D.S.I.R. Road Research Committee, whom we wish to thank for financial assistance and for their permission for publication.

THE DYSON PERRINS LABORATORY, OXFORD. [*Received, November 8th*, 1950.]

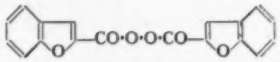
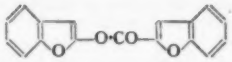
179. *Coumariloyl Peroxide and its Decomposition in Organic Solvents.*

By M. C. Ford and William A. Waters.

Coumariloyl peroxide has been prepared, and its decomposition studied. It does not appear to yield radicals capable of attacking carbon tetrachloride, benzene, chlorobenzene, or nitrobenzene.

During an investigation of methods for obtaining heterocyclic free radicals attention was turned to the diacyl peroxides derived from heterocyclic carboxylic acids. Peroxides of this type, which should undergo homolytic fission in the usual manner, have been little studied; furoyl peroxide (Milas and McAlevy, *J. Amer. Chem. Soc.*, 1934, **56**, 1219) and nicotinoyl peroxide (Milas and Panagiotakos, *ibid.*, 1940, **62**, 1878) have been prepared but their decompositions have not been investigated.

In the nitrogen-ring series, the formation of dimeric and polymeric forms of acid chlorides owing to their internal-salt formation makes the preparation of the corresponding diacyl peroxides difficult. However, in the oxygen-ring series no such internal-salt formation is possible, and in the one example in the literature (Milas and McAlevy, *loc. cit.*) the peroxide was obtained in good yield.

(I.)   (II.)

Coumariloyl peroxide (I) has now been prepared in 49% yield by an adaptation of the methods of von Pechmann and Vanino (*Ber.*, 1894, **27**, 1510) and Gelissen and Hermans (*Ber.*, 1925, **58**, 292), and its decomposition has been studied in a number of solvents (see Table II). In each case coumarilic acid was isolated, there was no observable attack upon the solvent, and the only other major product was an amorphous polymeric substance insoluble in light petroleum, sparingly soluble in ether, and partly soluble in hot aqueous sodium hydroxide.

From the decompositions of the peroxide in benzene and in carbon tetrachloride solution, small amounts (*ca.* 2·5%) of a yellow crystalline product of m. p. 124—125° were also obtained. On the basis of its analysis, its ultra-violet absorption, and the identification of coumarilic acid as a hydrolysis product, this was considered to be 2-(coumariloyloxy)coumarone (II).

It is significant that the decomposition did not appear to generate any radicals capable of attacking the solvents which have been examined. Thus, whereas the decomposition of a diaroyl peroxide, $(Ar{\cdot}CO_2)_2$, in carbon tetrachloride solution (Böeseken and Gelissen, *Rec. Trav. chim.*, 1924, **43**, 869) leads to the corresponding carboxylic acid, $Ar{\cdot}CO_2H$, only after hydrolysis of the ω-trichloro-derivative, $Ar{\cdot}CCl_3$, resulting from attack of the aryl radical upon the solvent, yet in the present case the reaction mixture after boiling with water contained no chloride ion. Again, in the decompositions of the peroxide in chlorobenzene and in nitrobenzene, both the crystalline and the amorphous reaction products were shown not to contain chlorine and nitrogen, respectively.

Thus, coumariloyl peroxide does not resemble in its behaviour the diaroyl peroxides which are easily capable of arylating benzene (Gelissen and Hermans, *Ber.*, 1925, **58**, 285), chlorobenzene, and nitrobenzene (Hey, *J.*, 1934, 1966), and the closest analogy is in that of cinnamoyl peroxide, whose decomposition in benzene solution was studied by Wieland and Rasuwajew (*Annalen*, 1930, **480**, 165), who could isolate only carbon dioxide, cinnamic acid, and what they believed to be polymeric styryl cinnamate.

This lack of attack upon the solvent is perhaps caused by the dominance of a radical-catalysed polymerisation of the αβ-unsaturated system present both in the coumariloyl peroxide and in any fragments resulting from its decomposition. However, the isolation of coumarilic acid in 26% yield from the decomposition of coumariloyl peroxide in carbon tetrachloride solution shows that hydrogen transfer between solute molecules and radicals must also occur to a considerable extent.

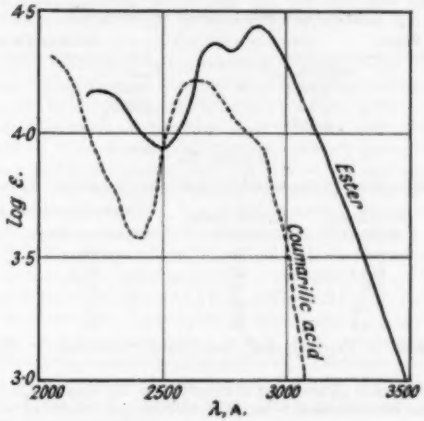
The decomposition of many aliphatic peroxides which can only yield free radicals of low intrinsic reactivity, *e.g.*, phenylacetyl peroxide (Bartlett and Leffler, *J. Amer. Chem. Soc.*, 1950, **72**, 3030), are similar to the above in that they do not lead to substitution of aromatic solvents, and we would suggest that in spite of the aromatic nature of the benzofuran ring system, coumariloyl peroxide should be classed with aliphatic rather than with aromatic diacyl peroxides.

Experimental.

(M. p.s are uncorrected. The elementary analysis is by Drs. Weiler and Strauss.)

Coumariloyl Chloride (cf. Stoermer and Calov, *Ber.*, 1901, **34**, 773).—Coumarilic acid (*Org. Synth.*, **24**, 33; 30 g.) was dried at 100°, treated with fresh phosphorus pentachloride (45 g.) (ice-cooling), and heated on the steam-bath until evolution of hydrogen chloride had ceased (1½ hours). Unless the acid was perfectly dry, an uncontrollable reaction set in at the start, with the formation of a black resin. The liquid mixture obtainable from dry materials was fractionated, coumariloyl chloride being collected at 267—269°/746 mm. as a pale yellow oil (26·2 g., 78%) which rapidly solidified (m. p. 54—55°).

Coumariloyl Peroxide.—The procedure of adding an ethereal solution of coumariloyl chloride to a stirred ice-cold partial solution of sodium peroxide in water is unsatisfactory owing to premature decomposition of the resulting alkaline hydrogen peroxide; the purity of the product thus obtained was only 81%, and the following method is preferable.



Aqueous sodium hydroxide (5N.; 30 ml.) and a solution of the acid chloride (23·6 g.) in sodium-dried ether (75 ml.) were dropped simultaneously into mechanically-stirred aqueous hydrogen peroxide (6·0%; 50 ml.) at 0° in such a way that the addition took 40 minutes and the solution was always just alkaline to phenolphthalein. After a further 1½ hours' stirring, the smell of the acid chloride had disappeared. The crude peroxide was collected (15 g.), dried in a vacuum ($CaCl_2$), and rapidly dissolved in chloroform (200 ml.) pre-heated to 50°. This solution was shaken with anhydrous magnesium sulphate and filtered, and the peroxide precipitated from the filtrate by dropwise addition of light petroleum (b. p. 60—80°; 400 ml.). The resulting *coumariloyl peroxide* (10·4 g., 49%) formed small, pale yellow needles which exploded at 117° and flashed violently in a flame (Found: equiv., 156·3. $C_{18}H_{10}O_6$ requires equiv., 161·1). The equivalent was determined by liberation of iodine in acetic anhydride solution (compare Vogel, "Practical Organic Chemistry," 1948, p. 766), and shows the purity to be 97%.

Decomposition of Coumariloyl Peroxide in Benzene Solution.—A solution of the peroxide (8·1 g.) in dry benzene ("AnalaR"; 50 ml.) was refluxed ($CaCl_2$ guard-tube) for 30 hours. Carbon dioxide was gradually evolved. On cooling, a small amount of solid separated; this was dissolved in more benzene, and the whole extracted repeatedly with aqueous sodium hydroxide (2N.). Acidification of the combined extracts gave a brown solid (2·7 g.) which when crystallised twice from toluene (charcoal) gave coumarilic acid, m. p. and mixed m. p. 187—189°.

The benzene layer was washed with water and dried (Na_2SO_4), and the benzene removed to give a brown gum (2·7 g.) of which only a trace was volatile in steam (2-phenylcoumarone is readily volatile; cf. Stoermer, *Ber.*, 1903, **36**, 3979). The residue from the steam-distillation was isolated with ether, the resulting gum dissolved in fresh ether (30 ml.), and filtered from tar, and the filtrate precipitated by an excess of light petroleum (b. p. 40—60°). A yellowish-brown amorphous solid was obtained which gave much tar in contact with solvents.

The mother-liquor on slow evaporation gave a yellow solid which, crystallised twice from methyl alcohol, gave 2-(*coumariloyloxy*)*coumarone* (0·22 g.) as yellow prisms, m. p. 124—125° (Found: C, 73·1; H, 3·62. $C_{17}H_{10}O_4$ requires C, 73·4; H, 3·62%). Its ultra-violet absorption in methyl alcohol is compared in Table I with that of coumarilic acid (both determined by Dr. F. B. Strauss). A comparison of the two curves (see figure) shows that no further conjugation is present in the ester. The structure was further confirmed by isolating coumarilic acid (0·1 g.), m. p. 192°, mixed m. p. 189—190°, as a product of the hydrolysis of this substance (0·4 g.) with aqueous alkali. The other component was phenolic (in aqueous solution it gave a clear violet colour with ferric chloride), and was probably *o*-hydroxyphenylacetic acid, but owing to its high solubility in water its isolation was impracticable with the amount of material available.

Decomposition of Coumariloyl Peroxide in Carbon Tetrachloride Solution.—A solution of the peroxide (12·5 g.) in purified carbon tetrachloride was refluxed for 20 hours. Carbon dioxide was gradually evolved and the solution slowly became dark brown. On cooling, coumarilic acid (2·8 g.) was precipitated together with a little tar. The acid immediately dissolved in cold N-sodium hydroxide, and after precipitation with dilute acid and crystallisation from aqueous alcohol and finally from toluene had m. p. and mixed m. p. 189—190°. A further quantity (2·5 g.) of this acid was obtained by extracting the carbon tetrachloride solution with 2N-sodium carbonate. After this extraction the carbon tetrachloride was evaporated and from the solid residue there were isolated, in the manner described above, 2-(coumariloyloxy)coumarone (0·3 g.; m. p. and mixed m. p. 126°) and polymeric material (3·2 g.).

In order to show that the coumarilic acid obtained in the preceding experiment did not arise from hydrolysis of chlorine-containing compounds, a separate decomposition reaction was carried out in similar circumstances, after which the whole of the initial reaction product was boiled with water for 6 hours: the resulting aqueous layer was shown not to contain chloride ions.

TABLE I.

Ultra-violet absorptions in methanol.

Ester.		Coumarilic acid.	
$\lambda_{max.}$, A.	$\log_{10} \varepsilon_{max.}$	$\lambda_{max.}$, A.	$\log_{10} \varepsilon_{max.}$
2250	4·17	2000	4·33
2650	4·36	2655	4·21
2875	4·425		

TABLE II.

Decomposition of coumariloyl peroxide in various solvents.

Solvent.	[Peroxide], moles/l.	Reflux time, hrs.	Yields (% of weight of peroxide taken). Alkali-soluble.[a]	Polymer.	Ester.
C_6H_6	0·5	30	33	31	2·5
C_6H_5Cl	0·4	20	36	48[b]	Traces
$C_6H_5{\cdot}NO_2$	0·6	20	23	25[c]	—
CCl_4	0·45	20	42	26[b]	2·5
n-C_6H_{14}	0·45	60	12	28	Traces

[a] Crude coumarilic acid. [b] Product does not contain chlorine. [c] Product does not contain nitrogen.

The other decompositions were carried out similarly and the results are tabulated. In each case the alkali-soluble portion was recrystallised twice from toluene and shown to be coumarilic acid by m. p. and mixed m. p.

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180. *Studies of Trifluoroacetic Acid. Part IV. The Use of 4 : 6-Benzylidene Trifluoroacetyl Methyl-α-D-glucopyranoside in the Synthesis of 2- and 3-Substituted Glucoses.*

By E. J. BOURNE, M. STACEY, (MRS.) C. E. M. TATLOW, and J. C. TATLOW.

Controlled methanolysis of 4 : 6-benzylidene 2 : 3-bistrifluoroacetyl α-methylglucoside (II) gives a 4 : 6-benzylidene trifluoroacetyl α-methylglucoside (III). From this compound both 2- and 3-substituted 4 : 6-benzylidene α-methylglucosides have been prepared. Whereas toluenesulphonation in pyridine gives the 2-tosyl 3-trifluoroacetyl derivative (V), acetylation in pyridine affords the 3-acetyl 2-trifluoroacetyl compound (VIII). However, by treatment with an acetic acid–trifluoroacetic anhydride mixture, the 2-acetyl 3-trifluoroacetyl derivative (XV) is obtained. Proof of the structures of these mixed esters is given and the migration of the trifluoroacetyl group is discussed.

IN Part II of this series (Bourne, Tatlow, and Tatlow, *J.*, 1950, 1367), the preparation and properties of certain trifluoroacetyl esters were described. These esters, which were prepared by treating the corresponding alcohols with trifluoroacetic anhydride in the presence of sodium trifluoroacetate, were shown to be very susceptible to hydrolysis and to methanolysis. Among the esters studied was 4 : 6-benzylidene 2 : 3-bistrifluoroacetyl α-methylglucoside (II), and it was found that this compound could be converted, in 98% yield, into 4 : 6-benzylidene α-methyl-

glucoside (I) simply by keeping it in methyl alcoholic solution (concentration *ca.* 1·2 g./100 c.c.) for 18 hours at room temperature. A further examination of this reaction has revealed that a crystalline intermediate compound, 4 : 6-benzylidene trifluoroacetyl α-methylglucoside (III), can be isolated when the reaction conditions are such that the compound separates from solution as it is formed. The requisite conditions may be attained either by using a concentrated solution (*ca.* 40 g./100 c.c.) of the bistrifluoroacetate in methyl alcohol, or by employing a methyl alcohol–carbon tetrachloride mixture, the mono-ester being only slightly soluble in carbon tetrachloride. The overall yield of 4 : 6-benzylidene trifluoroacetyl α-methylglucoside from 4 : 6-benzylidene α-methylglucoside can be improved three-fold if the unstable bistrifluoroacetate is not isolated.

A detailed examination of the mono-ester (III) was undertaken in order to locate the trifluoroacetoxy-group and to assess the value of the compound as a possible intermediate in the synthesis of either 2- or 3-substituted glucoses. This revealed the interesting fact that the mono-ester can give both 2- and 3-derivatives, depending on the reaction conditions. Further, the trifluoroacetyl residue has potential value as a readily removable blocking group suitable for general application in syntheses in the carbohydrate series.

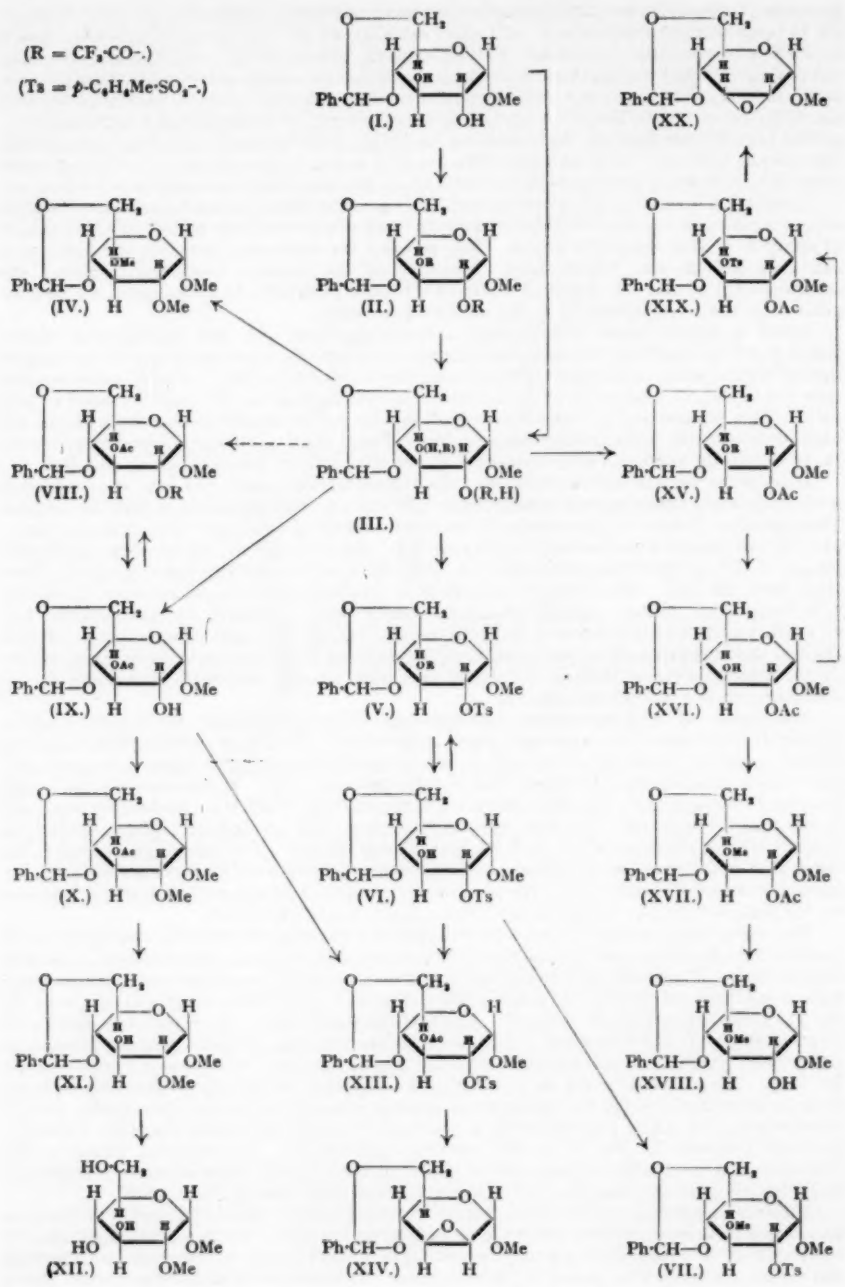
When 4 : 6-benzylidene trifluoroacetyl α-methylglucoside (III) was treated with methyl iodide and silver oxide for 3½ hours in an attempt to prepare the corresponding 4 : 6-benzylidene methyl trifluoroacetyl α-methylglucoside, methylation was incomplete. After a longer reaction time (40 hours), 4 : 6-benzylidene 2 : 3-dimethyl α-methylglucoside (IV) was recovered in 74% yield. This replacement of trifluoroacetyl groups by methyl groups during methylation has been observed with other trifluoroacetates, but the rate of the exchange is variable and seems to depend on the particular ester concerned and on the purity of the methylating reagents.

In contrast to the above exchange, the trifluoroacetyl group was not removed when 4 : 6-benzylidene trifluoroacetyl α-methylglucoside was toluenesulphonated in pyridine solution. The crystalline di-ester (V) thus produced was identical with that obtained by trifluoroacetylation of 4 : 6-benzylidene 2-tosyl α-methylglucoside (VI); the structure of (VI) has been established beyond doubt by Robertson and Griffith (*J.*, 1935, 1193) and by Bolliger and Prins (*Helv. Chim. Acta*, 1945, **28**, 465). Furthermore, hydrolysis of each sample of the mixed ester (V) yielded 4 : 6-benzylidene 2-tosyl α-methylglucoside, which was converted by methylation into 4 : 6-benzylidene 3-methyl 2-tosyl α-methylglucoside (VII) (Bolliger and Prins, *loc. cit.*). Despite the fact that a sharp melting point could not be obtained for the toluenesulphonation product of the trifluoroacetate, there is no doubt that this product was 4 : 6-benzylidene 2-tosyl 3-trifluoroacetyl α-methylglucoside (V).

Acetylation of 4 : 6-benzylidene trifluoroacetyl α-methylglucoside, by means of acetic anhydride in pyridine, gave a product which appeared to be an acetate-trifluoroacetate but was difficult to purify. However, on alcoholysis this product afforded a pure crystalline monoacetate, later shown to be 3-acetyl 4 :6-benzylidene α-methylglucoside (IX). A pure sample of the elusive 3-acetyl 4 : 6-benzylidene 2-trifluoroacetyl α-methylglucoside (VIII) was obtained by treatment of the 3-acetyl derivative (IX) with trifluoroacetic anhydride and sodium trifluoroacetate; on methanolysis of the mixed ester the 3-acetate was regenerated. The difficulties inherent in the removal of pyridine under anhydrous conditions from this relatively unstable acetate-trifluoroacetate undoubtedly explain why the pure di-ester could not be isolated when it was prepared by the acetylation of 4 : 6-benzylidene trifluoroacetyl α-methylglucoside.

The acetyl group of the acetyl 4 : 6-benzylidene α-methylglucoside (IX) was allocated to position 3 on the basis of the behaviour of the compound during both methylation and toluenesulphonation. Treatment with methyl iodide and silver oxide gave a product which was identical with a specimen of 3-acetyl 4 : 6-benzylidene 2-methyl α-methylglucoside (X) prepared by Dr. D. J. Bell (unpublished method). This methylation product was obtained in dimorphic forms having m. p. 128·5° and 145°. The lower-melting form was obtained first, but subsequent experiments yielded the more stable higher-melting form, which was the one synthesised by Dr. Bell. The material having m. p. 128·5° ultimately changed into the higher-melting form. Both forms were converted by deacetylation into the same crystalline 4 : 6-benzylidene methyl α-methylglucoside (XI), identical with a specimen of 4 : 6-benzylidene 2-methyl α-methylglucoside prepared by Dr. D. J. Bell (method unpublished). Furthermore, graded acidic hydrolysis of the 4 : 6-benzylidene methyl α-methylglucoside (XI) afforded the well-characterised 2-methyl α-methylglucoside (XII) (Haworth, Hirst, and Teece, *J.*, 1931, 2858).

Toluenesulphonation of the above acetyl 4 : 6-benzylidene α-methylglucoside in pyridine gave 3-acetyl 4 : 6-benzylidene 2-tosyl α-methylglucoside (XIII), which was obtained also by acetylation of 4 : 6-benzylidene 2-tosyl α-methylglucoside (VI) and on treatment with sodium methoxide afforded the known 4 : 6-benzylidene 2 : 3-anhydro-α-methylmannoside (XIV)


(R = $CF_3 \cdot CO$-.)
(Ts = p-$C_6H_4Me \cdot SO_2$-.)
(I.)
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(XX.)

(Robertson and Griffith, *loc. cit.*). Thus, unless migration of the acetyl group had occurred during both the methylation and the toluenesulphonation reactions, a possibility which we consider to be quite unlikely when these results are studied in conjunction with those reported later for the 2-acetate series, acetic anhydride in pyridine had introduced an acetyl group at position 3 of 4 : 6-benzylidene trifluoroacetyl α-methylglucoside.

When 4 : 6-benzylidene trifluoroacetyl α-methylglucoside was acetylated by an alternative procedure, *viz.*, by treatment with a mixture of acetic acid and trifluoroacetic anhydride (cf. Bourne, Stacey, Tatlow, and Tedder, *J.*, 1949, 2976), there was obtained a new crystalline acetate-trifluoroacetate, designated as 2-acetyl 4 : 6-benzylidene 3-trifluoroacetyl α-methylglucoside (XV). By methanolysis this yielded a second acetyl 4 : 6-benzylidene α-methylglucoside (XVI), which was characterised as the 2-acetate by methylation and by toluenesulphonation.

The acetyl methyl compound (XVII), which was obtained when the new acetate (XVI) was treated with silver oxide and methyl iodide, was hydrolysed to 4 : 6-benzylidene 3-methyl α-methylglucoside (XVIII), the structure of which has been established by Bolliger and Prins (*loc. cit.*). Toluenesulphonation of the acetyl 4 : 6-benzylidene α-methylglucoside (XVI) gave 2-acetyl 4 : 6-benzylidene 3-tosyl α-methylglucoside (XIX), as was shown by its subsequent conversion into 4 : 6-benzylidene 2 : 3-anhydro-α-methylalloside (XX) (cf. Robertson and Griffith, *loc. cit.*).

Thus it can be seen that 4 : 6-benzylidene trifluoroacetyl α-methylglucoside can be converted into (i) 4 : 6-benzylidene 2-tosyl 3-trifluoroacetyl α-methylglucoside by treatment with toluene-*p*-sulphonyl chloride in pyridine, (ii) 3-acetyl 4 : 6-benzylidene 2-trifluoroacetyl α-methylglucoside by treatment with acetic anhydride in pyridine, and (iii) 2-acetyl 4 : 6-benzylidene 3-trifluoroacetyl α-methylglucoside by treatment with acetic acid–trifluoroacetic anhydride. These striking observations may be explained in three ways: first, that the monotrifluoroacetate was a mixture of the isomeric 2- and 3-esters; secondly, that it possessed an ortho-ester structure; and thirdly, that migration of the trifluoroacetyl group occurred during one or more of the esterification reactions. The first possibility can be eliminated as the sole explanation, since the yields of the purified products of the reactions (i), (ii), and (iii) were 78%, at least 64% (based upon the yield of 3-acetyl 4 : 6-benzylidene α-methylglucoside), and 64%, respectively. Although the second possibility appeared unlikely in view of the *trans*-orientation of the 2- and 3-hydroxy-groups of the glucose molecule, evidence concerning the structure of the trifluoroacetate (III) was sought from measurements of its infra-red absorption spectrum. These measurements (see figure), carried out in collaboration with Dr. D. H. Whiffen, afforded strong evidence of the presence of a carbonyl group, and, therefore, of the probable absence of an ortho-ester structure. Hence the explanation of the experimental facts surely must lie in the migration of the trifluoroacetyl group.

Since it is known that the migration of acyl groups is favoured by alkaline conditions (for a summary see Pacsu, *Adv. Carbohydrate Chem.*, 1945, **1**, 77), it is probable that migration did not occur during the acetic acid–trifluoroacetic anhydride acetylation process, and thus that the 4 : 6-benzylidene trifluoroacetyl α-methylglucoside carried its ester group on position 3. It would appear therefore that migration of the trifluoroacetyl group occurred during the acetylation reaction in pyridine, but not during toluenesulphonation in the same medium. The behaviour of trifluoroacetate esters during methanolysis (Bourne, Tatlow, and Tatlow, *loc. cit.*) suggests their ready participation in acyl migration reactions, since both reactions involve an exchange of alkoxy-groups on a single trifluoroacetyl group. If this be so, then the trifluoroacetyl group may well be displaced, when necessary, to enable the incoming group to take up its more favoured position. This hypothesis explains the apparent anomaly that two series of products are obtained from the esterifications conducted in pyridine. It is an established fact that toluenesulphonation of 4 : 6-benzylidene α-methylglucoside proceeds preferentially at position 2 (Robertson and Griffith, *loc. cit.*; Bolliger and Prins, *loc. cit.*), whereas, if the usual migrations of acetyl groups (*i.e.*, away from the potential reducing group) be any guide (cf. Hirst and Peat, *Ann. Reports*, 1934, **31**, 172; Brown, Hough, and Jones, *J.*, 1950, 1125), the 3-acetate should be more stable than its 2-isomer. The greater lability, during methanolysis, of the acetate group of 2-acetyl 4 : 6-benzylidene 3-trifluoroacetyl α-methylglucoside (XV) compared with that of 3-acetyl 4 : 6-benzylidene 2-trifluoroacetyl α-methylglucoside (VIII) furnished some confirmation of this view.

Two main conclusions may be drawn from this work: first, that 4 : 6-benzylidene trifluoroacetyl α-methylglucoside is a new and useful intermediate for the synthesis of both 2- and 3-substituted glucoses, and, secondly, that the use of a carboxylic acid–trifluoroacetic anhydride

acylating medium possesses advantages over the more common pyridine process in cases where alkali-sensitive groupings are already present in the carbohydrate molecule. The extension of this study of acylation, using the carboxylic acid–trifluoroacetic anhydride process and other methods, to other partly trifluoroacetylated carbohydrates may well lead to the preparation of hitherto inaccessible derivatives, and this possibility is now being examined.

Experimental.

Precautions.—Unless otherwise stated, all operations involving trifluoroacetates were conducted with dry reagents under anhydrous conditions.

Preparation of 4 : 6-*Benzylidene* α-*Methylglucoside.*—Prepared by the method of Freudenberg, Toepffer, and Andersen (*Ber.*, 1928, **61**, 1750), this compound had m. p. 164° and $[\alpha]_D^{19}$ +114° (*c*, 0·55 in chloroform).

Preparation of 4 : 6-*Benzylidene* 2 : 3-*Bistrifluoroacetyl* α-*Methylglucoside.*—This bistrifluoroacetate was obtained from 4 : 6-benzylidene α-methylglucoside by the method of Bourne, Tatlow, and Tatlow (*loc. cit.*); it had m. p. 88—89°, $[\alpha]_D^{18}$ +77·6° (*c*, 0·80 in carbon tetrachloride).

Partial Methanolysis of 4 : 6-*Benzylidene* 2 : 3-*Bistrifluoroacetyl* α-*Methylglucoside.*—Methyl alcohol (2·0 c.c.), dried with magnesium and iodine as described by Vogel (" A Text-book of Practical Organic Chemistry," Longmans, Green & Co., 1948, 168), was added to a solution of the bistrifluoroacetate (0·900 g.) in carbon tetrachloride (4·0 c.c.). On being kept at room temperature, the solution gradually precipitated a solid, which was removed by filtration and proved to be 4 : 6-*benzylidene trifluoroacetyl* α-*methylglucoside* (0·503 g., 70%), m. p. 211° (unchanged by recrystallisation from carbon tetrachloride), $[\alpha]_D^{19}$ +119° (*c*, 1·60 in chloroform) (Found: C, 50·4; H, 4·5; F, 15·0; OMe, 8·5; CF_3·CO, 26·1%; *M*, 355. $C_{14}H_{17}O_7F_3$ requires C, 50·8; H, 4·5; F, 15·1; OMe, 8·2; CF_3·CO, 25·65%; *M*, 378).

Direct Preparation of 4 : 6-*Benzylidene Trifluoroacetyl* α-*Methylglucoside.*—4 : 6-Benzylidene α-methylglucoside (10·0 g.) was added to a mixture of trifluoroacetic anhydride (20·0 c.c.) and sodium trifluoroacetate (1·078 g.). When the initial vigour of the reaction had abated, the mixture was distilled under diminished pressure with several portions of carbon tetrachloride, and the residue was exhaustively extracted with the same solvent. The filtered extracts were distilled under diminished pressure and, before crystallisation commenced, the residual syrupy bistrifluoroacetate was dissolved in warm magnesium-dried methyl alcohol (35 c.c.). A crystalline precipitate soon separated from the solution. After 15 minutes, carbon tetrachloride (100 c.c.) was added and the solid removed by filtration. A further quantity of the product was recovered by concentrating the mother-liquors. The combined solids were recrystallised from carbon tetrachloride giving 4 : 6-benzylidene trifluoroacetyl α-methylglucoside (8·57 g., 64%), m. p. 211° (alone and on admixture with the specimen mentioned above), $[\alpha]_D^{21}$ +119° (*c*, 1·46 in chloroform). In three similar experiments yields of 51, 53, and 64% were obtained. Only under controlled conditions can reproducible values be obtained for the m. p. of this compound, because (*a*) the compound tends to sublime and (*b*) the m. p. depends on the time of heating.

Methylation of 4 : 6-*Benzylidene Trifluoroacetyl* α-*Methylglucoside.*—Silver oxide (0·260 g.) was added to a solution of the monotrifluoroacetate (0·350 g.) in methyl iodide (15·0 c.c.), and the mixture was refluxed for 20 hours. The methyl iodide was removed by distillation, and the residue exhaustively extracted with carbon tetrachloride. The filtered extracts were evaporated and the residual glucoside was remethylated as before. Recrystallisation of the product from light petroleum (b. p. 100—120°) afforded 4 : 6-benzylidene 2 : 3-dimethyl α-methylglucoside (0·211 g., 74%), m. p. and mixed m. p. 122°, $[\alpha]_D^{18}$ +98° (*c*, 0·43 in acetone) (Found: C, 62·0; H, 7·1; OMe, 29·95. Calc. for $C_{14}H_{22}O_6$: C, 61·9; H, 7·1; OMe, 30·0%). Irvine and Scott (*J.*, 1913, **103**, 575) give m. p. 122—123° and $[\alpha]_D^{20}$ +97° (*c*, 1·64 in acetone) for this compound.

From a second experiment, in which the methylation reaction was allowed to proceed for only 3½ hours, a mixture was obtained. A portion of this material, after acidic hydrolysis, was submitted to filter-paper chromatography with a butanol solvent, as described by Hirst, Hough, and Jones (*J.*, 1949, 928). An aniline hydrogen phthalate spray (Partridge, *Nature*, 1949, **164**, 443) revealed two spots, having R_F values corresponding to those of glucose and a monomethyl glucose, respectively.

4 : 6-*Benzylidene* 2-*Tosyl* 3-*Trifluoroacetyl* α-*Methylglucoside from* 4 : 6-*Benzylidene* 2-*Tosyl* α-*Methylglucoside.*—4 : 6-Benzylidene 2-tosyl α-methylglucoside (0·938 g.), prepared according to Robertson and Griffith's method (*loc. cit.*), was added to a mixture of sodium trifluoroacetate (0·264 g.), trifluoroacetic anhydride (5·50 c.c.), and carbon tetrachloride (25·0 c.c.). After being refluxed for 75 minutes, by which time complete dissolution had been achieved, the mixture was distilled under diminished pressure with four portions (15 c.c. each) of carbon tetrachloride. The residue was extracted exhaustively with boiling carbon tetrachloride and the filtered extracts were distilled, leaving a residue, which, after recrystallisation from light petroleum (b. p. 100—120°), afforded 4 : 6-*benzylidene* 2-*tosyl* 3-*trifluoroacetyl* α-*methylglucoside* (0·724 g., 64%), m. p. 180—185° (unchanged by further crystallisation), $[\alpha]_D^{20}$ +44·0° (*c*, 5·0 in chloroform) (Found: OMe, 5·9; CF_3·CO, 18·0. $C_{23}H_{23}O_9SF_3$ requires OMe, 5·8; CF_3·CO, 18·2%).

4 : 6-*Benzylidene* 2-*Tosyl* 3-*Trifluoroacetyl* α-*Methylglucoside from* 4 : 6-*Benzylidene Trifluoroacetyl* α-*Methylglucoside.*—Toluene-*p*-sulphonyl chloride (0·302 g.) was added to a solution of 4 : 6-benzylidene trifluoroacetyl α-methylglucoside (0·502 g.) in pyridine (2·0 c.c.). After 2 days at room temperature, the reaction mixture was distilled under diminished pressure with three portions (15·0 c.c. each) of trichloroethylene. The residue was exhaustively extracted with boiling trichloroethylene, and the filtered extracts were distilled under diminished pressure. The residue, recrystallised from light petroleum (b. p. 100—120°), gave 4 : 6-benzylidene 2-tosyl 3-trifluoroacetyl α-methylglucoside (0·550 g., 78%), m. p. 176—182° (not depressed on admixture with the specimen previously obtained), $[\alpha]_D^{21}$ +46·7° (*c*, 1·46 in chloroform) (Found: OMe, 6·1; CF_3·CO, 18·1. $C_{23}H_{23}O_9SF_3$ requires OMe, 5·8; CF_3·CO, 18·2%).

Hydrolysis of 4 : 6-*Benzylidene* 2-*Tosyl* 3-*Trifluoroacetyl* α-*Methylglucoside*.—The titration-liquors from the trifluoroacetyl estimation on the sample of 4 : 6-benzylidene 2-tosyl 3-trifluoroacetyl α-methylglucoside, which had been prepared by toluenesulphonation of 4 : 6-benzylidene trifluoroacetyl α-methylglucoside, were made slightly alkaline to phenolphthalein and the acetone was removed under diminished pressure. The solid thus precipitated was recrystallised from aqueous alcohol containing a trace of ammonia. The product, obtained in 97% yield, had m. p. 155° [alone and on admixture with authentic 4 : 6-benzylidene 2-tosyl α-methylglucoside (Robertson and Griffith, *loc. cit.*)], $[\alpha]_D^{18}$ +59·5° (*c*, 1·21 in chloroform) (Found : C, 57·95; H, 5·7. Calc. for $C_{21}H_{24}O_8S$: C, 57·8; H, 5·5%). Methylation with silver oxide and methyl iodide gave a product (yield, 50%) having m. p. 155—156°, not depressed on admixture with authentic 4 : 6-benzylidene 3-methyl 2-tosyl α-methylglucoside supplied by Dr. J. Dewar. Bolliger and Prins (*loc. cit.*) give m. p. 156—157° for this compound.

In a similar fashion, the other sample of 4 : 6-benzylidene 2-tosyl 3-trifluoroacetyl α-methylglucoside afforded 4 : 6-benzylidene 2-tosyl α-methylglucoside in 86% yield.

Preparation of 3-*Acetyl* 4 : 6-*Benzylidene* α-*Methylglucoside*.—Acetic anhydride (0·80 c.c.) was added to a solution of 4 : 6-benzylidene trifluoroacetyl α-methylglucoside (2·014 g.) in pyridine (4·50 c.c.). After 36 hours at room temperature, the reaction mixture was distilled under diminished pressure with several portions of chloroform and carbon tetrachloride. The residual syrup was dissolved in warm ethyl alcohol, which was removed immediately by distillation at 60° (bath-temp.)/12 mm., leaving a white solid. Recrystallisation from light petroleum (b. p. 100—120°) gave 3-*acetyl* 4 : 6-*benzylidene* α-*methylglucoside* (1·086 g., 64%), m. p. 174°, $[\alpha]_D^{14}$ +110° (*c*, 0·85 in chloroform) (Found : C, 59·3; H, 6·3; OMe, 9·7; Ac, 12·9. $C_{16}H_{20}O_7$ requires C, 59·3; H, 6·2; OMe, 9·6; Ac, 13·3%). In two similar experiments the same product was isolated in yields of 56 and 60%, severally.

3-*Acetyl* 4 : 6-*Benzylidene* 2-*Trifluoroacetyl* α-*Methylglucoside from* 3-*Acetyl* 4 : 6-*Benzylidene* α-*Methylglucoside*.—The 3-acetate (0·507 g.) was heated at 50° for 10 minutes with a mixture of sodium trifluoroacetate (0·052 g.) and trifluoroacetic anhydride (3·5 c.c.). The reaction mixture was distilled under diminished pressure with four portions of carbon tetrachloride (15 c.c. each), and the residue was extracted with light petroleum (20 c.c.; b. p. 40—60°). When cooled, the filtered extract deposited long needles of 3-*acetyl* 4 : 6-*benzylidene* 2-*trifluoroacetyl* α-*methylglucoside* (0·372 g., 57%), m. p. 107—109° (unchanged by recrystallisation), $[\alpha]_D^{20}$ +125·0° (*c*, 0·61 in carbon tetrachloride) (Found : C, 51·4; H, 4·6%; N-alkali uptake, 4·84 c.c./g. $C_{18}H_{19}O_8F_3$ requires C, 51·45; H, 4·6%; N-alkali uptake, 4·76 c.c./g.). The low yield may be attributed, in some measure, to the relative instability of the compound and also to its high solubility in organic solvents. By concentration of the titration-liquors from the acyl estimation 4 : 6-benzylidene α-methylglucoside, m. p. 165°, $[\alpha]_D^{20}$ +114° (*c*, 0·56 in chloroform), was isolated in 83% yield.

Methanolysis of 3-*Acetyl* 4 : 6-*Benzylidene* 2-*Trifluoroacetyl* α-*Methylglucoside*.—A solution of 3-acetyl 4 : 6-benzylidene 2-trifluoroacetyl α-methylglucoside (0·070 g.), prepared as above, in magnesium-dried methyl alcohol (10·0 c.c.), was refluxed for 35 minutes before the solvent was removed at 12 mm. pressure. The residue (0·054 g., 100%) had m. p. 174°, alone and on admixture with the sample of 3-acetyl 4 : 6-benzylidene α-methylglucoside already obtained.

Attempted Preparation of 3-*Acetyl* 4 : 6-*Benzylidene* 2-*Trifluoroacetyl* α-*Methylglucoside from* 4 : 6-*Benzylidene Trifluoroacetyl* α-*Methylglucoside*.—Acetic anhydride (0·55 c.c.) was added to a solution of 4 : 6-benzylidene trifluoroacetyl α-methyiglucoside (2·090 g.) in pyridine (7·0 c.c.), and the mixture was kept at room temperature for 36 hours. The volatile material was removed by distillation under diminished pressure with light petroleum (b. p. 100—120°), and the residue recrystallised from light petroleum (b. p. 40—60°). The product (1·798 g.), m. p. 80—95°, was recrystallised again from light petroleum (b. p. 40—60°) and then had m. p. 88—92°. This material could not be purified further by repeated crystallisation (Found : F, 12·9. $C_{18}H_{19}O_8F_3$ requires F, 13·6%).

Preparation of 3-*Acetyl* 4 : 6-*Benzylidene* 2-*Methyl* α-*Methylglucoside*.—Silver oxide (1·25 g.) was added to a solution of 3-acetyl 4 : 6-benzylidene α-methylglucoside (0·670 g.) in methyl iodide (25·0 c.c.), and the mixture was refluxed for 18 hours. The methyl iodide was removed by distillation, and the residue extracted exhaustively with boiling chloroform. Distillation of the filtered extracts left a crystalline solid, which, when recrystallised from light petroleum (b. p. 60—80°), afforded 3-acetyl 4 : 6-benzylidene 2-methyl α-methylglucoside (0·487 g., 70%), m. p. 128·5°, $[\alpha]_D^{14}$ +81·9° (*c*, 0·92 in chloroform) (Found : C, 60·1; H, 6·5; OMe, 18·4; Ac, 13·1. Calc. for $C_{17}H_{22}O_7$: C, 60·3; H, 6·6; OMe, 18·3; Ac, 12·7%). Two similar experiments gave the same compound, m. p. 128°.

From a fourth experiment, the product, isolated in 70% yield, had m. p. 145° [alone and on admixture with a specimen of 3-acetyl 4 : 6-benzylidene 2-methyl α-methylglucoside (m. p. 145°) supplied by Dr. D. J. Bell], $[\alpha]_D^{18}$ +82·5° (*c*, 0·61 in chloroform) (Found : C, 60·6; H, 6·7; OMe, 18·2%). Subsequent experiments invariably yielded the higher-melting material.

The two products isolated from these experiments appeared to be polymorphic forms of the same compound, the higher-melting form being the more stable. A mixture of the two had m. p. 145°. All the material having m. p. 128·5° ultimately changed into the higher-melting form.

Preparation of 4 : 6-*Benzylidene* 2-*Methyl* α-*Methylglucoside*.—A small piece of sodium was added to a solution of 3-acetyl 4 : 6-benzylidene 2-methyl α-methylglucoside (m. p. 128·5°; 0·102 g.) in magnesium-dried methyl alcohol (10·0 c.c.), and the solution was kept for 18 hours at room temperature. The solvent was distilled off under diminished pressure and water was added to the residue. The aqueous suspension was extracted with chloroform. The washed extracts were dried ($MgSO_4$), filtered, and distilled, leaving a residue, which, after recrystallisation from light petroleum (b. p. 60—80°), had m. p. 168° (alone and on admixture with an authentic specimen of 4 : 6-benzylidene 2-methyl α-methylglucoside supplied by Dr. D. J. Bell), $[\alpha]_D^{17}$ +78·9° (*c*, 1·19 in ethyl alcohol) (Found : C, 60·7; H, 6·8; OMe, 21·15. Calc. for $C_{15}H_{20}O_6$: C, 60·8; H, 6·8; OMe, 20·95%). Yield, 0·051 g. (57%).

In a similar fashion, the other polymorphic form (m. p. 145°) of 3-acetyl 4 : 6-benzylidene 2-methyl

α-methylglucoside gave 4 : 6-benzylidene 2-methyl α-methylglucoside in 79% yield, m. p. 167° (Found : C, 60·5; H, 7·0; OMe, 20·9%). This compound did not depress the m. p. of the specimen already prepared or of Bell's authentic compound, but it did depress the m. p. of a specimen of 4 : 6-benzylidene 3-methyl α-methylglucoside (m. p. 147°) supplied by Dr. H. R. Bolliger.

Preparation of 2-Methyl α-Methylglucoside.—4 : 6-Benzylidene 2-methyl α-methylglucoside (0·552 g.) was refluxed for 30 minutes with a mixture of ethyl alcohol (55 c.c.) and 0·1N-sulphuric acid (5·0 c.c.). The solution was neutralised with barium carbonate, and the barium salts were separated on the centrifuge. The supernatant liquid was steam-distilled under reduced pressure and then concentrated to dryness. Recrystallised twice from ethyl acetate, the product (0·114 g., 29%) had m. p. 146—148° (alone and on admixture with an authentic specimen of 2-methyl α-methylglucoside supplied by Dr. D. J. Bell), $[\alpha]_D^{20}$ +153° (*c*, 0·46 in water) (Found : C, 46·35; H, 7·9; OMe, 29·8. Calc. for $C_8H_{16}O_6$: C, 46·15; H, 7·75; OMe, 29·8%). Haworth, Hirst, and Teece (*loc. cit.*) give m. p. 147—148° and $[\alpha]_D^{19}$ +155° (in water) for this compound.

3-Acetyl 4 : 6-Benzylidene 2-Tosyl α-Methylglucoside from 4 : 6-Benzylidene 2-Tosyl α-Methylglucoside.—Acetic anhydride (0·30 c.c.) was added to a solution of 4 : 6-benzylidene 2-tosyl α-methylglucoside (0·104 g.) in pyridine (5·0 c.c.). After being kept at room temperature for 36 hours, the reaction mixture was poured into water, and the solid thus precipitated was recrystallised from ethyl alcohol. The product, *3-acetyl 4 : 6-benzylidene 2-tosyl α-methylglucoside* (0·078 g., 69%), had m. p. 160—162°, $[\alpha]_D^{18}$ +51·2° (*c*, 0·76 in chloroform) (Found : C, 57·9; H, 5·6; S, 6·3; OMe, 6·4. $C_{23}H_{26}O_8S$ requires C, 57·7; H, 5·5; S, 6·7; OMe, 6·5%).

3-Acetyl 4 : 6-Benzylidene 2-Tosyl α-Methylglucoside from 3-Acetyl 4 : 6-Benzylidene α-Methylglucoside.—Toluene-*p*-sulphonyl chloride (0·473 g.) was added to 3-acetyl 4 : 6-benzylidene α-methylglucoside (0·515 g.) in pyridine (7·0 c.c.), and the solution was kept at room temperature for 4 days, before being poured into ice-water containing hydrochloric acid. The precipitated solid (0·774 g.) was crystallised from alcohol, giving 3-acetyl 4 : 6-benzylidene 2-tosyl α-methylglucoside (0·618 g., 81%), m. p. 160—162° (alone and on admixture with the specimen already obtained), $[\alpha]_D^{18}$ +49·1° (*c*, 2·90 in chloroform) (Found : C, 57·6; H, 5·5; S, 6·5; OMe, 6·5. $C_{23}H_{26}O_8S$ requires C, 57·7; H, 5·5; S, 6·7; OMe, 6·5%).

Preparation of 4 : 6-Benzylidene 2 : 3-Anhydro-α-methylmannoside.—3-Acetyl 4 : 6-benzylidene 2-tosyl α-methylglucoside (0·228 g.), prepared from the 3-acetate, was refluxed for 2 hours with a solution of sodium (0·166 g.) in magnesium-dried methyl alcohol (8·5 c.c.) and then water (10·0 c.c.) was added. When cooled, the solution deposited crystalline 4 : 6-benzylidene 2 : 3-anhydro-α-methylmannoside (0·093 g., 74%), m. p. and mixed m. p. 146°, $[\alpha]_D^{17}$ +103·0° (*c*, 0·81 in chloroform) (Found : C, 63·3; H, 6·1. Calc. for $C_{14}H_{16}O_5$: C, 63·6; H, 6·1%). Robertson and Griffith (*loc. cit.*) cite m. p. 146—147° and $[\alpha]_D^{15}$ +107·4° (*c*, 1·61 in chloroform) for this compound.

Preparation of 2-Acetyl 4 : 6-Benzylidene 3-Trifluoroacetyl α-Methylglucoside.—A mixture of glacial acetic acid (0·160 c.c.) and trifluoroacetic anhydride (0·60 c.c.) was added to 4 : 6-benzylidene trifluoroacetyl α-methylglucoside (0·730 g.) in benzene (7·0 c.c.). After 20 minutes at 60°, carbon tetrachloride (20 c.c.) was added and the solution was evaporated under reduced pressure. The residue was re-acetylated as before for 15 minutes, and the reaction mixture was distilled under diminished pressure with four portions (20 c.c. each) of carbon tetrachloride. Recrystallised twice from light petroleum (b. p. 40—60°), *2-acetyl 4 : 6-benzylidene 3-trifluoroacetyl α-methylglucoside* (0·515 g., 64%) had m. p. 134—135°, $[\alpha]_D^{27}$ +94·5° (*c*, 1·00 in carbon tetrachloride) (Found : C, 51·55; H, 4·8%; N-alkali uptake, 4·78 c.c./g. $C_{18}H_{19}O_8F_3$ requires C, 51·45; H, 4·6%; N-alkali uptake, 4·76 c.c./g.). By concentration of the titration-liquors from the acyl estimation, 4 : 6-benzylidene α-methylglucoside, m. p. 164—165°, $[\alpha]_D^{19}$ +114° (*c*, 0·59 in chloroform), was isolated in 74% yield.

Preparation of 2-Acetyl 4 : 6-Benzylidene α-Methylglucoside.—A solution of 2-acetyl 4 : 6-benzylidene 3-trifluoroacetyl α-methylglucoside (0·410 g.) in magnesium-dried methyl alcohol (20 c.c.) was kept at 50° for 2 minutes before the alcohol was removed by distillation [50° (bath-temp.)/12 mm.]. Recrystallisation of the product from light petroleum (b. p. 60—80°) gave *2-acetyl 4 : 6-benzylidene α-methylglucoside* (0·263 g., 83%), m. p. 133—134°, $[\alpha]_D^{19}$ +112° (*c*, 0·86 in chloroform) (Found : C, 59·2; H, 6·4; Ac, 12·9. $C_{14}H_{20}O_7$ requires C, 59·3; H, 6·2; Ac, 13·3%). A mixture with 2-acetyl 4 : 6-benzylidene 3-trifluoroacetyl α-methylglucoside had m. p. 105—115°. From the titration-liquors of the acetyl estimation, 4 : 6-benzylidene α-methylglucoside, m. p. and mixed m. p. 165—166°, $[\alpha]_D^{21}$ +113° (*c*, 0·78 in chloroform), was isolated in 57% yield.

This methanolysis was repeated several times with approximately the same quantities of the reagents, and similar results were obtained. Attempts to carry out the conversion on a larger scale (three-fold or greater) invariably gave an impure product which could not be purified.

Preparation of 2-Acetyl 4 : 6-Benzylidene 3-Methyl α-Methylglucoside.—A solution of 2-acetyl 4 : 6-benzylidene α-methylglucoside (0·352 g.) in methyl iodide (15·0 c.c.) was refluxed for 19 hours with silver oxide (0·261 g.). The methyl iodide was removed by distillation and the residue was extracted with boiling chloroform. Evaporation of the extract left a residue, which was re-treated with methyl iodide and silver oxide. The product was isolated as before and twice recrystallised from light petroleum (b. p. 60—80°), giving *2-acetyl 4 : 6-benzylidene 3-methyl α-methylglucoside* (0·159 g., 43%), m. p. 121°, $[\alpha]_D^{23}$ +101·0° (*c*, 0·80 in chloroform) (Found : C, 60·2; H, 6·5; Ac, 12·9. $C_{17}H_{22}O_7$ requires C, 60·3; H, 6·6; Ac, 12·7%).

Preparation of 4 : 6-Benzylidene 3-Methyl α-Methylglucoside.—The titration-liquors from the acetyl estimation on 2-acetyl 4 : 6-benzylidene 3-methyl α-methylglucoside were made just alkaline to phenolphthalein and concentrated under diminished pressure, before being extracted with chloroform. The extracts were dried ($MgSO_4$), filtered, and evaporated. The residue was crystallised from light petroleum (b. p. 60—80°), giving 4 : 6-benzylidene 3-methyl α-methylglucoside in 65% yield, m. p. 147° [alone and on admixture with an authentic specimen (m. p. 147°; cf. Bolliger and Prins, *loc. cit.*) supplied by Dr. H. R. Bolliger], $[\alpha]_D^{22}$ +123·0° (*c*, 0·45 in tetrachloroethane) (Found : C, 60·9; H, 6·75. Calc. for

$C_{18}H_{20}O_6$: C, 60·8; H, 6·8%). The m. p. of this compound was depressed by the specimen of 4 : 6-benzylidene 2-methyl α-methylglucoside already obtained.

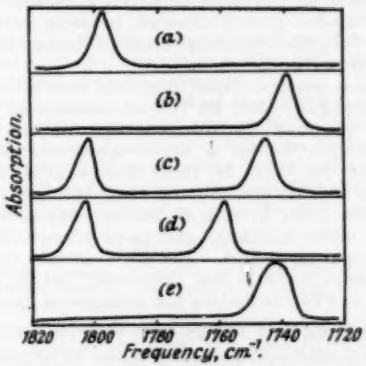
Preparation of 2-Acetyl 4 : 6-Benzylidene 3-Tosyl α-Methylglucoside.—Toluene-*p*-sulphonyl chloride (0·296 g.) was added to a solution of 2-acetyl 4 : 6-benzylidene α-methylglucoside (0·487 g.) in pyridine (4·0 c.c.), and the mixture kept at room temperature for 4 days. The solution was poured into a water–chloroform mixture, the chloroform layer was separated, and the aqueous phase was extracted with three further portions of chloroform. The combined chloroform extracts were washed with water, very dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and water again, before being dried ($MgSO_4$ and $NaHCO_3$), filtered, and distilled. The residual syrup was recrystallised from aqueous alcohol and gave *2-acetyl 4 : 6-benzylidene 3-tosyl α-methylglucoside* (0·347 g., 49%), m. p. 120—121°, $[\alpha]_D^{28}$ +28·1° (*c*, 0·78 in chloroform) (Found : C, 57·8; H, 5·5; S, 6·8%; N-sodium methoxide uptake, 3·92 c.c./g. $C_{25}H_{28}O_9S$ requires C, 57·7; H, 5·5; S, 6·7%; N-sodium methoxide uptake, 4·18 c.c./g.).

Preparation of 4 : 6-Benzylidene 2 : 3-Anhydro-α-methylalloside.—A solution of 2-acetyl 4 : 6-benzylidene 3-tosyl α-methylglucoside (0·0276 g.) in methanolic sodium methoxide (1·00 c.c.; 0·20N.) was refluxed for 45 minutes. Addition of water (5·0 c.c.) caused precipitation of 4 : 6-benzylidene 2 : 3-anhydro-α-methylalloside (0·0120 g., 79%), m. p. and mixed m. p. 199—200°, $[\alpha]_D^{28}$ +144·0° (*c*, 0·23 in chloroform) (Found : C, 63·75; H, 5·9. Calc. for $C_{14}H_{14}O_5$: C, 63·6; H, 6·1%). Robertson and Griffith (*loc. cit.*) cite m. p. 199—200° and $[\alpha]_D^{18}$ +140·4° (*c*, 2·21 in chloroform) for this compound.

Analytical Methods.—(a) *Trifluoroacetyl and acetyl determinations.* These determinations were carried out by the method described by Bourne, Tatlow, and Tatlow (*loc. cit.*).

(b) *Fluorine determination.* The method, which involved fusion with sodium in a bomb of special design and determination of the resultant fluoride ion as lead chlorofluoride, was that of Belcher and Tatlow (J. C.) (unpublished).

(c) *Carbon and hydrogen determination in the presence of fluorine.* The usual combustion was modified by the inclusion of a sodium fluoride packing to absorb any silicon tetrafluoride formed (Belcher and Goulden, unpublished).



Infra-red Absorption Spectra (*with* D. H. Whiffen).—Infra-red absorption spectra of the following compounds were determined in chloroform solution (*c*, 2—3) : (*a*) 4 : 6-benzylidene trifluoroacetyl α-methylglucoside, (*b*) 3-acetyl 4 : 6-benzylidene α-methylglucoside, (*c*) 2-acetyl 4 : 6-benzylidene 3-trifluoroacetyl α-methylglucoside, (*d*) 3-acetyl 4 : 6-benzylidene 2-trifluoroacetyl α-methylglucoside, (*e*) 2 : 3-diacetyl 4 : 6-benzylidene α-methylglucoside. The results are shown graphically in the accompanying figure with the corresponding lettering.

Very strong evidence of the presence of carbonyl groups is given in each case, since only the carbonyl stretching frequency commonly gives rise to a strong infra-red band between 1700 and 1800 cm.$^{-1}$. Each acetate-trifluoroacetate shows two absorption peaks, at about 1750 and 1800 cm.$^{-1}$, respectively, and thus the different strengths of the two carbonyl groups in each of these compounds are demonstrated. The frequencies of the absorption peaks accord with those of the mono-esters (*a* and *b*) and with those reported by Hartwell, Richards, and Thompson (*J.*, 1948, 1436) for the carbonyl groups in methyl acetate (1742 cm.$^{-1}$, in chloroform) and ethyl trichloroacetate (1768 cm.$^{-1}$, as a liquid).

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181. *Lanosterol. Part XI. Reduction of Ketones in the Lanosterol Series.*

By J. F. Cavalla and J. F. McGhie.

Reduction of acetoxylanostenedione with lithium aluminium hydride gave diacetoxylanostanone, whilst acetoxylanostanedione yielded diacetoxylanostanol. Oxidation of the last with chromic acid gave diacetoxylanostanone, which could be hydrolysed to the corresponding ketolanostanediol.

Reduction of the inert double bond in lanostadienol * derivatives was first reported by one of us (J. F. McG.) with Dorée and Kurzer (Part V, *J.*, 1948, 988). It was shown that reduction of acetoxylanostenedione and lanostenedione by zinc and acetic acid, zinc amalgam and hydrochloric acid, sodium and *iso*propyl alcohol, or catalytically, gave the corresponding fully saturated compounds, acetoxylanostanedione and lanostanedione. This work had in view the eventual preparation of the parent hydrocarbon, lanostane, by the further reduction of the products to the corresponding polyalcohols, then dehydration, followed by catalytic reduction, to give lanostane (cf. the degradation of cholic acid to cholane; Wieland *et al.*, *Z. physiol. Chem.*, 1912, **80**, 287).

Whilst this work was in progress Voser, Montavon, Gunthard, Jeger, and Ruzicka (*Helv. Chim. Acta*, 1950, **33**, 1893) reported the preparation of lanostane as follows: Acetoxylanostanedione and ethane-1 : 2-dithiol gave a monomercaptal, which on reduction with Raney nickel gave the monoketonic derivative, acetoxylanostanone. Hydrolysis and then mild oxidation of the resulting alcohol gave a diketone, isomeric with lanostanedione described above but differing in that both the keto-groups could be reduced by zinc amalgam and hydrochloric acid to yield the hydrocarbon lanostane.

In view of this publication, our own experiments and findings in this field, already briefly recorded elsewhere (*Chem. and Ind.*, 1950, **46**, 744) are summarised below.

Acetoxylanostenedione, prepared by the oxidation of either lanostenyl acetate or γ-lanostadienyl acetate (formerly known as dihydroagnosteryl acetate) with chromic acid (Marker *et al.*, *J. Amer. Chem. Soc.*, 1937, **59**, 1368; Ruzicka *et al.*, *Helv. Chim. Acta*, 1944, **27**, 472), or with ozone (Dorée and McGhie, *Nature*, 1944, **153**, 148), or by hydrogen peroxide (Birchenough, Thesis, London, 1950; Voser *et al.*, *loc. cit.*), was more conveniently prepared by the modified method, from either lanostenyl acetate or γ-lanostadienyl acetate and chromic acid, described in the experimental section. The diketo-acetate formed deep yellow needles (sometimes plates) and gave a curve in the ultra-violet having a well-defined absorption maximum at 275 mμ. (log ε, 3·94), indicating the presence of an unsaturated 1 : 4-diketone system $\cdot CO\cdot\overset{|}{C}\overset{|}{\cdot}C\cdot CO\cdot$, the inert ethylenic linkage lying between two quaternary carbon atoms. The assumption that no bond migration took place in the formation of acetoxylanostanedione (McGhie, Thesis, London, 1947) received support from recent spectroscopic evidence (Roth and Jeger, *Helv. Chim. Acta*, 1949, **32**, 1620).

The only available information on the reduction of such an unsaturated 1 : 4-diketone was from the results of Lutz and Gillespie (*J. Amer. Chem. Soc.*, 1950, **72**, 2002), who have shown that either *cis*- or *trans*-dibenzoylethylene with lithium aluminium hydride gave, as the principal product, the saturated 4-keto-1 : 4-diphenylbutanol, together with a small quantity of the unsaturated (*trans*-)1 : 4-glycol. Reduction beyond the keto-alcohol stage did not take place although an excess of lithium aluminium hydride was present in the reaction mixture. Further reduction of the keto-alcohol with either platinum and hydrogen or lithium aluminium hydride led to a mixture of the saturated stereoisomeric 1 : 4-diols.

Acetoxylanostenedione, when treated with lithium aluminium hydride, under conditions analogous to those used by Lutz and Gillespie, gave a mixture of stereoisomeric alcohols from which a small yield of a compound, m. p. 215°, $[\alpha]_D^{20}$ +53·0°, could be isolated. Formulation of this compound as a ketodiol appears likely since on treatment with acetic anhydride it afforded a keto-diacetate, m. p. 175—176°, $[\alpha]_D^{20}$ +58·4°.

Subsequently it was found more convenient to acetylate the mixture of alcohols, whereafter two products could be isolated by fractional crystallisation followed by chromatographic purification. The first had m. p. 175—176°, $[\alpha]_D^{20}$ +59·0°, identical with the compound prepared as described above. The second had m. p. 200°, $[\alpha]_D^{20}$ +57·5°, and appears to be an

* See footnote, p. 744.

unsaturated triacetate. Hydrolysis of this compound did not give a crystalline triol; it gives a faint yellow colour with tetranitromethane and may contain the grouping AcO·CH·C:C·CH·OAc. These results are in agreement with those of Lutz and Gillespie (*loc. cit.*). Also present in the acetylated mixture of alcohols, although in very small yield, was a saturated alcohol, m. p. 237—238°, identical with the compound obtained by acetylating the product of reduction of acetoxylanostanedione by lithium aluminium hydride.

It was thought that acetoxylanostanedione, being fully saturated, should give less complex results than those found for acetoxylanostenedione. Reduction of this by the same procedure gave a mixture of alcohols which on fractional crystallisation gave a minute yield of a crystalline product, m. p. 219—220°. This, at first, was thought to be unchanged acetoxylanostanedione (m. p. 222—224°) but analysis showed it to be a triol. Further work to confirm such a hypothesis had to be abandoned owing to the paucity of the material available. Acetylation of the mixed alcohols followed by crystallisation gave good yields of a compound, m. p. 239°, $[\alpha]_D^{20}$ +70·0°, analytical figures for which agreed well with those of a hydroxy-diacetate. [Since this work was completed, Voser *et al.* (*loc. cit.*) have reported the preparation of what appears to be the same compound by virtually an identical process.] The presence of an unacetylated hydroxyl group was confirmed by oxidation of the hydroxy-diacetate with chromic acid, a keto-diacetate, m. p. 176—177°, $[\alpha]_D^{20}$ +58·4°, together with an acid fraction which has not yet given crystalline material, being isolated. Hydrolysis of the hydroxy-diacetate, m. p. 239°, gave no crystalline product, though hydrolysis of the keto-diacetate, m. p. 176—177°, gave a keto-diol, m. p. 215—216°, $[\alpha]_D^{20}$ +53·6°. The identity between these two compounds and those obtained by the direct reduction of acetoxylanostenedione was shown by the further reduction of all four with lithium aluminium hydride to an alcohol mixture which on acetylation gave the hydroxy-diacetate, m. p. 239°. Further evidence of the reduction of the inert double bond in acetoxylanostenedione by lithium aluminium hydride was given by the identification of very small amounts of the hydroxy-diacetate, m. p. 239°, in the acetate mixture obtained by acetylating the mixture of alcohols from the reduction.

In a search for alternative methods of isolating the reduction products from acetoxylanostanedione, the mixture of alcohols was boiled with acetic anhydride, a product, m. p. 213—214°, $[\alpha]_D^{20}$ +83·4°, being obtained. This is an unsaturated diacetate giving a yellow colour with tetranitromethane. Attempts to prepare this compound from the hydroxy-diacetate, m. p. 239°, by dehydration with boiling acetic anhydride were unsuccessful. Treatment with phosphorus oxychloride in hot pyridine, however, gave the unsaturated diacetate in good yield.

Experimental.

All m. p.s are uncorrected. Specific rotations were measured in chloroform solution at 20°. Aluminium oxide used in chromatographic work was from Messrs. Peter Spence Ltd. (Grade "0"). All analyses are by Drs. Weiler and Strauss, Oxford.

Acetoxylanostenedione.—Lanostenyl acetate (20 g.) in glacial acetic acid (1 l.) was treated at 95° with excess of chromic acid (12 g.; in 30 ml. of water), in a three-necked flask with mechanical stirring. The chromic acid was added dropwise during 30 minutes with constant stirring and the temperature maintained for a further 1½ hours. The dark green reaction mixture was poured into 4 l. of ice-water, the excess of chromic acid destroyed with dilute sulphurous acid, sodium chloride added to coagulate the oxidation product, and the latter filtered off. This crude yellow material was dissolved in ether (500 ml.) and the solution washed with water till free from chromium salts. Washing with dilute sodium hydroxide solution gave a small acid fraction (1 g.) which could not be obtained crystalline. The ethereal layer was washed till neutral, then dried (Na_2SO_4), and the solvent removed to leave a pale yellow solid. Passage of this material through a short alumina column, using benzene as carrier, followed by crystallisation from methanol, gave glistening yellow plates (12 g.) of acetoxylanostenedione, m. p. 158—159°, $[\alpha]_D^{20}$ +91·6° (*c* 0·024), identical with an authentic specimen. Reduction of the mother-liquors gave a small quantity (1 g.) of a less pure material.

Acetoxylanostanedione.—This compound was prepared by reducing acetoxylanostenedione with zinc dust and glacial acetate acid (Dorée, McGhie, and Kurzer, *J.*, 1948, 988). Good yields (80%) were obtained of the colourless plates, m. p. 222—224°, $[\alpha]_D^{20}$ +55·4° (*c* 0·04), identical with an authentic specimen kindly supplied by Dr. F. Kurzer.

Reduction of Acetoxylanostenedione.—In all reductions using lithium aluminium hydride, absolute ether was used. The most satisfactory way of achieving this was found to be drying the ether with calcium hydride.

A solution of acetoxylanostenedione (2 g.) in absolute ether (100 ml.) was added dropwise, with efficient mechanical stirring, to a cooled suspension of lithium aluminium hydride (1·7 g.) in absolute ether (100 ml.) under reflux. As soon as the yellow ketone solution met the hydride the colour disappeared and a white solid was precipitated. The stirring was continued for 1 hour after addition of the diketone. The flask containing the reaction mixture was placed in ice, and ice-water added with great caution to the vigorously stirred suspension; the mixture gelled transitorily and the ether boiled. Once the initial reaction was over cold dilute sulphuric acid was added. Two layers which separated

were transferred to a separatory funnel where the ethereal layer was well washed with water and dried (Na_2SO_4). The solvent was removed, to leave a white amorphous product, very soluble in methanol. Crystallisation from small volumes of methanol gave a mixture of white amorphous powder (which could not be purified further) and hard well-defined crystals, m. p. 211—213°, which were separated by hand. Three further crystallisations from very small volumes of methanol gave large plates of *lanostanonediol*, m. p. 215°, $[\alpha]_D^{20}$ +53·0° (*c*, 0·038) (Found: C, 78·0; H, 11·3. $C_{30}H_{52}O_2$ requires C, 78·2; H, 11·4%). Mild acetylation of this product with acetic anhydride and pyridine at room temperature for 8 hours gave *diacetoxylanostanone*, m. p. 175—176°, $[\alpha]_D^{20}$ +58·4° (*c*, 0·018) (Found: C, 75·1; H, 10·3. $C_{34}H_{56}O_5$ requires C, 75·0; H, 10·4%). Attempts at chromatographic separation of the mixed alcohols met with little success and the method of direct crystallisation was adhered to.

A further reduction of acetoxylanostenedione (2 g.) with lithium aluminium hydride (1·7 g.) provided a mixture of alcohols which was kept at 100° for 2½ hours with acetic anhydride (25 ml.) and pyridine (5 ml.). The usual working up gave an oily white solid which was crystallised from methanol (20 ml.) to give a white product (1 g.) crystallising in felting needles, m. p. 185—190°. Adsorption on an alumina column (10 × 1·3 cm.) from light petroleum (b. p. 60—80°) followed by elution with benzene–light petroleum (b. p. 60—80°) (1 : 1; 200 ml.) gave a white product, crystallising in felting needles (from methanol), m. p. 198—199°. Two further crystallisations gave *triacetoxylanostene*, m. p. 200°, $[\alpha]_D^{20}$ +57·5° (*c*, 0·049) (Found: C, 74·1; H, 9·9. $C_{36}H_{56}O_6$ requires C, 73·7; H, 9·9%). With tetranitromethane, this compound gave a pale yellow colour.

Hydrolysis, using 6% alcoholic potassium hydroxide, gave an amorphous product similar to that obtained from the original reduction, from which no crystalline compound could be obtained.

The methanolic mother-liquor from the crude triacetoxylanostene gave a colourless glass on removal of the solvent. This was adsorbed on alumina (15 × 1·3 cm.) from light petroleum (b. p. 60—80°, 200 ml.) and eluted to give the following fractions: (*a*) light petroleum (b. p. 60—80°; 300 ml.), 0·2 g. of oil; (*b*) light petroleum (b. p. 60—80°)–benzene (1·1; 250 ml.), 0·4 g. of oil; (*c*) benzene (250 ml.), 0·08 g. of oil; (*d*) chloroform (250 ml.), trace of oil.

Fraction (*a*) gave, on crystallisation from methanol, felted needles, m. p. 192—195°, which on two recrystallisations gave triacetoxylanostene, m. p. 199—200°, undepressed on admixture with authentic material.

Fraction (*b*), crystallised from methanol, gave hard plates, m. p. 172°, raised by two recrystallisations to m. p. 175°. This was identical with diacetoxylanostanone obtained by acetylation of lanostanonediol, m. p. 215—216°.

Fraction (*c*), recrystallised from methanol gave felted needles, m. p. 217—221°, which on two recrystallisations gave m. p. 237—238°. This was diacetoxylanostanol, identical with that obtained by reduction of acetoxylanostanedione with lithium aluminium hydride followed by acetylation.

Hydrolysis of fraction (*b*) with 5% alcoholic potassium hydroxide gave good yields of lanostanonediol, m. p. 215—216°.

Reduction of Diacetoxylanostanone and Lanostanonediol.—These compounds (0·2 g.) in absolute ether (50 ml.) were severally treated with lithium aluminium hydride (0·5 g.) in absolute ether (50 ml.). In each case the resultant mixed alcohols were acetylated and the product crystallised from acetone–methanol, to give diacetoxylanostanol (0·15 g.), m. p. 238—239°, identical with that obtained by reduction of acetoxylanostanedione.

Reduction of Acetoxylanostanedione.—A solution of acetoxylanostanedione (4 g.) in absolute ether (200 ml.) was treated with a stirred suspension of lithium aluminium hydride (3·4 g.) in absolute ether (100 ml.) in the manner described for the reduction of acetoxylanostenedione. More ether was required owing to the smaller solubility of the saturated compound in this solvent. Working up gave a white amorphous solid which was adsorbed from light petroleum (b. p. 60—80°)–benzene (1 : 1; 350 ml.) on alumina (13 × 1·3 cm.). Elution of the column with light petroleum (b. p. 60—80°)–benzene (1 : 1), benzene alone, or benzene–ether (1 : 1) gave products which could not be crystallised. Final elution of the column with ether alone (200 ml.) gave a small quantity (50 mg.) of a white solid which had m. p. 216—217° after crystallisation from methanol. Two further crystallisations gave fine needles of *lanostanetriol*, m. p. 219—220° (Found: C, 78·0; H, 11·6. $C_{30}H_{54}O_3$ requires C, 77·9; H, 11·8%). Mild acetylation of this alcohol (10 mg.) with acetic anhydride–pyridine (1 : 1; 2 ml.) failed to give a solid product.

Acetylation of the Mixed Alcohols.—The product from a further reduction of acetoxylanostanedione (4 g.) was kept at 100° for 2 hours with acetic anhydride (40 ml.) and pyridine (10 ml.). The mixture was then poured into water and the white solid precipitated was extracted with ether in the usual manner. Removal of the solvent and crystallisation of the residue from acetone (60 ml.)–methanol (30 ml.) gave long felted needles, m. p. 235—236° (3 g.). Two recrystallisations from the same mixture of solvents gave the pure *diacetoxylanostanol*, m. p. 239°, $[\alpha]_D^{20}$ +70·0° (*c*, 0·025) (Found: C, 74·7; H, 10·5. $C_{34}H_{58}O_5$ requires C, 74·7; H, 10·7%). Reduction of the mother-liquors from the purification gave a further yield (0·4 g.) of impure material which had m. p. 237° after two crystallisations. No other product could be obtained.

A further reduction of acetoxylanostanedione (1·5 g.) gave the typical mixture of alcohols which was boiled for 2 hours with acetic anhydride (35 ml.) and poured into water. Extraction of the white solid with ether and removal of the solvent gave an oily white solid. This was adsorbed from light petroleum (b. p. 60—80°; 300 ml.) on a column of alumina (10 × 1·3 cm.). Elution of the column gave the following fractions: (*a*) light petroleum (b. p. 60—80°; 600 ml.), trace of oil; (*b*) light petroleum (b. p. 60—80°)–benzene (1 : 1; 250 ml.), 0·5 g. of colourless oil; (*c*) benzene (250 ml.), 0·4 g. of white solid; (*d*) benzene (250 ml.), 0·1 g. of white solid; (*e*) chloroform (250 ml.), 0·2 g. of white solid.

Fraction (*b*) gave hard colourless plates, m. p. 208—209°, on crystallisation from acetone–methanol.

Three further crystallisations gave pure *diacetoxylanostene*, m. p. 213—214°, $[\alpha]_D^{20}$ +83·4° (*c*, 0·020). This compound gave a yellow colour with tetranitromethane and was practically insoluble in methanol (Found: C, 77·4; H, 10·6. $C_{34}H_{56}O_4$ requires C, 77·2; H, 10·7%).

Dehydration of Diacetoxylanostanol.—With acetic anhydride. Diacetoxylanostanol (0·2 g.) was boiled for 1 hour with acetic anhydride (20 ml.) and pyridine (3 ml.). The solution was poured into water and extracted with ether to leave, on removal of the solvent, an oily white solid. Crystallisation from acetone (4 ml.) and methanol (20 ml.) gave fine felting needles (0·15 g.), m. p. 237—238°, undepressed on admixture with diacetoxylanostanol. From the mother-liquors only crude starting material could be obtained.

With phosphorus oxychloride. Diacetoxylanostanol (0·9 g.) in dry pyridine (50 ml.) was treated at 100° with phosphorus oxychloride (4 ml.) for 1 hour. The mixture was poured into water and extracted with ether, and the ethereal layer washed with dilute hydrochloric acid to remove pyridine. Continued washing with dilute sodium carbonate solution and water till neutral, followed by removal of the solvent, gave a hard white solid. Crystallisation from acetone–methanol gave small rectangular plates (0·65 g.), m. p. 212—214°. Two recrystallisations from the same solvent mixture gave pure diacetoxylanostene, m. p. 213—214°, $[\alpha]_D^{20}$ +83·9° (*c*, 0·049), identical with the material prepared as above.

Hydrolysis. Diacetoxylanostanol (0·25 g.) was refluxed with a solution of potassium hydroxide (2 g.) in alcohol (50 ml.) for 1½ hours, poured into water, and extracted with ether. Removal of the solvent gave an oily white solid from which no crystalline product could be isolated by fractional crystallisation or chromatography.

Oxidation of Diacetoxylanostanol.—Diacetoxylanostanol (1·8 g.) in glacial acetic acid (100 ml.) was treated, at 45—50° with stirring, with a solution of chromic acid (1·8 g.) in 90% acetic acid (20 ml.). The temperature was maintained for 1 hour and the mixture poured into water; dilute sulphurous acid was added to destroy the excess of chromic acid. The precipitated white solid was extracted with ether, and the ethereal layer washed with water to free it from chromium salts. Extraction of the ether solution with 2N-sodium hydroxide gave an acid fraction which has not yet been isolated in the pure state. Methylation, using diazomethane, of the crude acid, followed by chromatography, has given only oils. The neutral fraction was washed, then dried (Na_2SO_4), and the ether removed to leave a colourless glass (1 g.). Crystallisation from acetone (3 ml.) and methanol (15 ml.) gave stout plates, m. p. 181—185°. These were adsorbed from light petroleum (b. p. 60—80°, 200 ml.) on alumina (13 × 1·3 cm.). Light petroleum (b. p. 60—80°)–benzene (1 : 1, 500 ml.) eluted pure *diacetoxylanostanone*, m. p. 176—177°, $[\alpha]_D^{20}$ +58·4° (*c*, 0·022) (Found: C, 74·9; H, 10·1. $C_{34}H_{54}O_5$ requires C, 75·0; H, 10·4%). Elution of the column with chloroform gave a small quantity of felting needles, m. p. 236°. These were unoxidized diacetoxylanostanol. The mixed m. p. of this ketone obtained by the oxidation of diacetoxylanostanol with the ketone obtained by acetylation of the alcohol obtained by reduction of acetoxylanostenedione was 176°.

Hydrolysis. Diacetoxylanostanone (0·25 g.) was refluxed for 2½ hours with a solution of potassium hydroxide (2·5 g.) in alcohol (50 ml.) and poured into water. Extraction with ether, followed by removal of the solvent, gave a coloured solid, which crystallised from aqueous methanol in large plates, m. p. 213—214°. Two further crystallisations from small volumes of methanol gave pure *ketolanostanediol*, m. p. 215—216°, $[\alpha]_D^{20}$ +53·6° (*c*, 0·030) (Found: C, 77·9; H, 11·2. $C_{30}H_{52}O_2$ requires C, 78·2; H, 11·4%). Reacetylation of this product gave plates of diacetoxylanostanone, m. p. 175—177°. The mixed m. p. of the above alcohol obtained by hydrolysis of diacetoxylanostanone with the alcohol obtained by the reduction of acetoxylanostenedione was 215°.

Reduction of Diacetoxylanostanone and Ketolanostanediol.—Diacetoxylanostanone and ketolanostanediol (0·25 g.) were severally reduced with lithium aluminium hydride (0·5 g.). Acetylation of the products, followed by crystallisation, gave in each case, diacetoxylanostanol, m. p. 237°, alone and on admixture with an authentic specimen.

The authors are indebted to Mr. P. Barker for the specific rotations. One of them (J. F. C.) acknowledges the award of a Department of Scientific and Industrial Research maintenance grant.

CHELSEA POLYTECHNIC, MANRESA ROAD, S.W.3. [*Received, November 30th*, 1950.]

NOTES.

182. *Refrachor: A New Physical Constant.*

By S. S. JOSHI and G. D. TULI.

A NEW physical constant for which we propose the name refrachor and the symbol [*F*] has been obtained by associating parachor (*P*) with refractive index (n_D^{20}) according to the expression $[F] = -P \log (n_D^{20} - 1)$. As a result of a study of a large number of compounds, we find that the observed refrachor of any compound is made up of two constants, one dependent on the atoms and the other on structural factors such as type of linkage, size of rings, etc. Some of the atomic, group, and structural refrachors derived by us are given in the Table. In deriving these, we have used throughout the parachor and refractive index values given by Vogel (*J.*, 1934, 333, 4758; 1938, 1323; 1940, 171, 1528; 1943, 636; 1946, 133; 1948, 607,

1804) and have adopted the procedure employed by him in the calculation of atomic and structural parachors.

Atomic, Structural, and Group Refrachors.

Atom, structure, or group.	Refrachor.	Atom, structure, or group.	Refrachor.
CH_2	12·89	I (aliphatic)	9·67
C (in CH_2)	−25·27	I (aromatic)	15·94
H (in CH_2)	19·08	Double bond (C:C)	28·70
O (in aliphatic ethers)	6·62	Triple bond (C$\vdots$C)	60·18
OH (in aliphatic alcohols)	11·09	Three-carbon ring	22·55
CO (in ketones)	7·88	Four-carbon ,,	21·48
CO_2 (in esters)	17·64	Five-carbon ,,	17·15
CO_2H	25·6	Six-carbon ,,	13·05
Cl (aliphatic)	20·5	Me	31·83
Cl (aromatic)	25·53	Ph	41·94
Br (aliphatic)	16·51	NO_2 (nitro)	25·84
Br (aromatic)	22·80	NO_2 (nitrite)	35·64

As slight structural variations result in marked differences in refrachors, the constant may prove more useful than the parachor alone when applied to problems of chemical constitution. A few cases in which its utility has been studied so far are outlined below.

1. *Determination of the Percentage of Tautomers in their Equilibrium Mixture at* 20°.—For keto–enol tautomeric mixtures the difference between the calculated refrachors of the two forms is large (12·44 units), whereas it is quite small in the case of parachor (1·4 units) and molecular refractivity (1·08). Percentage composition calculated from refrachor determinations is quite comparable with values obtained from chemical methods (Conant and Thompson, *J. Amer. Chem. Soc.*, 1932, **54**, 4039; Meyer, *Ber.*, 1912, **45**, 2850).

Compound.	[*F*], obs.	[*F*], calc. Keto.	[*F*], calc. Enol.	Enol, %, calc.	Enol, %, chemically found.
Ethyl acetoacetate	114·0	114·96	102·52	7·7	7·3 (Conant); 7·4 (Meyer)
Acetylacetone	83·30	92·31	79·87	72·4	76·5 (Conant); 76·0 (Meyer)
1 : 1-Diacetylethane	101·2	105·06	92·62	31·02	31·2 (Meyer)

2. *Distinction between Stably Linked and Reactive Halogen Atoms.*—Two sets of refrachor values are obtained for halogen atoms, according as they are reactive as in alkyl halides, etc., or are stably linked as in halogenated benzenes, etc. Comparison of observed and calculated refrachor values for, say, a halogenated homologue of benzene shows whether the halogen is in the nucleus or in the side chain. Similarly, in benzene derivatives in which halogen atoms are made reactive by other groups, *e.g.*, nitro, the refrachor values for the halogen atoms approach that of " aliphatic halogen " as the number of activating groups increases.

3. *Refrachor and Structural Variations.*—Isomeric groups and compounds in which the mode of linking of multivalent atoms is different show appreciable differences in their refrachors. Thus the refrachor values for the nitro and the nitrite group are 25·84 and 35·64, respectively, and for two double bonds and one triple bond are 57·4 and 60·18, respectively, whereas the parachor values for the same are 73·8, 75·3, 39·8, and 40·6, respectively. Refrachor can, therefore, prove of considerable help in the study of the structure of isomeric compounds.

Further work with this constant for determination of the type of linkage and elucidation of other structural problems is in progress.

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183. *The Freezing-point Diagram of the Hydrazine–Water System.*

By T. C. H. Hill and J. F. Sumner.

The cryoscopy of the hydrazine–water system has been studied by Semishin (*J. Gen. Chem., Russia*, 1938, **8**, 654). Mohr and Audrieth (*J. Phys. Coll. Chem.*, 1949, **53**, 901) have conducted a fuller investigation, yet have not covered the complete range owing to difficulties encountered at lower temperatures. We have covered the whole range, the results showing a maximum corresponding to the monohydrate and two eutectic points.

Experimental.—Hydrazine–water mixtures of an approximate pre-determined composition were prepared, and the f. p. determined in each case. An accurate determination of the hydrazine content was then made.

The apparatus (Fig. 1) consisted of a Pyrex tube (*A*) (4·5″ × 1″), fitted with a two-hole bung of polyvinyl chloride, which carried a calibrated alcohol thermometer (*B*) and a glass stirrer (*C*) supported in the cross-unit of a T-piece (*D*). The thermometer was calibrated by using it to determine in the apparatus the freezing point of pure water (0·0°), aniline (−6·4°), carbon tetrachloride (−22·95°), mercury (−38·86°), and chloroform (−63·3°). A correction curve was drawn and extrapolated slightly at both ends. For the four temperatures between −78° and −84°, comparison with an N.P.L.-standardised spirit thermometer was allowed to suffice. The third unit of *D* was connected to a supply of dry, oxygen-free nitrogen. An outer jacket (*F*) was provided, into which could be inserted the tube *A*, held in position by a split ring of polyvinyl chloride. By way of an inlet tube sealed in the bottom of *F*, a stream of dry air could be passed.

For a determination, 15 ml. of the hydrazine–water mixture were prepared in the tube *A*, and the thermometer and stirrer inserted. A slow stream of nitrogen was admitted, so as to preclude the introduction of atmospheric oxygen and moisture during stirring, and the liquid was carefully frozen by immersion in a cooling bath. For temperatures down to −70°, an acetone–solid carbon dioxide mixture was found to be satisfactory, and for lower temperatures an ethyl alcohol–liquid nitrogen mixture.

Fig. 1.

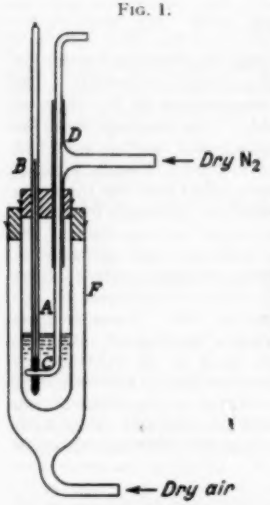
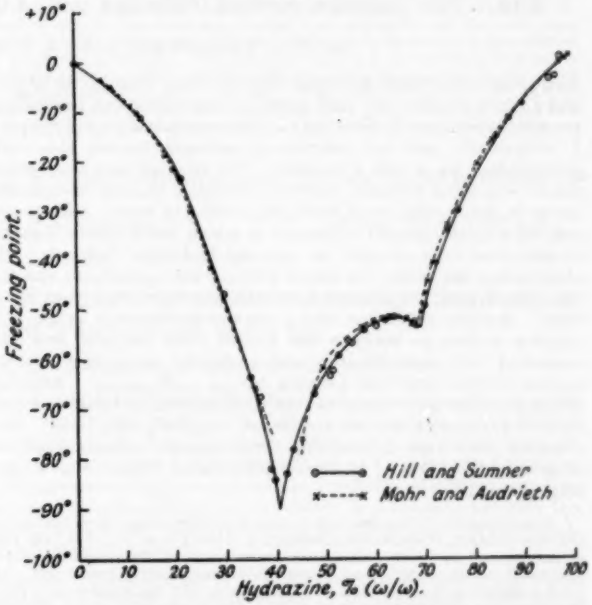


Fig. 2.



The freezing process being complete, the tube was transferred to the jacket *F*, and the temperature allowed to rise slowly. Condensation of moisture on the inner wall of *F*, and on the outer wall of *A*, was prevented by the passage of dry air. The freezing point of the solution was taken as the temperature at which the last trace of solid disappeared.

Some difficulty was at first experienced in ascertaining freezing points which occurred below −70° owing to the viscous nature of the system. However, this was satisfactorily surmounted after practice.

The contents of *A* were then allowed to attain room temperature, and a sample was withdrawn for analysis. The hydrazine content was determined iodometrically by Kolthoff's method (*J. Amer. Chem. Soc.*, 1924, **46**, 2009).

Results.—The values obtained are shown in the Table.

Freezing points of hydrazine–water mixtures.

N_2H_4, % (w/w) ...	0·0	13·3	21·4	29·8	34·9	36·8	38·9	39·6	42·1
F. p. ...	0·0°	−11·0°	−23·4°	−46·7°	−63·6°	−67·3°	−82°	−84°	−83°
N_2H_4, % (w/w) ...	43·3	47·7	50·9	51·6	52·9	54·7	55·4	57·9	60·5
F. p. ...	−78°	−66·7°	−63·1°	−61·8°	−58·9°	−56·0°	−56·5°	−54·1°	−53·2°
N_2H_4, % (w/w) ...	62·2	63·9	68·0	70·1	77·0	87·7	95·6	96·9	97·8
F. p. ...	−52·0°	−51·4°	−52·4°	−49·2°	−29·8°	−11·2°	− 3·4°	− 2·8°	+ 1·2°

Plotting the hydrazine concentration (% by wt.) against the f. p. of the solution (Fig. 2) shows a maximum at −51·5°, the concentration of hydrazine (64·0%) corresponding to the monohydrate,

N_2H_4,H_2O. Two eutectics are recorded, one at N_2H_4 40·5% (f. p. −90°), and the other at N_2H_4 69·3% (f. p. −53·5°).

The figures obtained by the authors correspond in general with those quoted by Mohr and Audrieth (*loc. cit.*) (cf. Fig. 2). The American investigators have not, however, effected a precise determination of the position of the water-rich eutectic. It is in this part of the diagram that the greatest difference occurs between the two sets of results.

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MINISTRY OF SUPPLY, WALTHAM ABBEY, ESSEX. [*Received, October 25th*, 1950.]

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184. *The Reaction between Diborane and Anhydrous Hydrazine.*

By H. J. EMELÉUS and F. G. A. STONE.

ANHYDROUS hydrazine has been found to react with excess of diborane at 0° to form hydrogen and a white hygroscopic solid which was involatile and insoluble in a variety of solvents. The reactants combined in unusually variable proportions in different experiments ($B_2H_6 : N_2H_4 = 1 : 0{\cdot}78$—$0{\cdot}97$), and the amount of hydrogen formed also varied. This suggests that the product may have been a mixture. The simplest and most probable initial reaction would be one in which the nitrogen atoms of hydrazine became co-ordinated to borine radicals, forming either $H_3B{\cdot}NH_2{\cdot}NH_2$ or $H_3B{\cdot}NH_2{\cdot}H_2N{\cdot}BH_3$, or both. Such products might well lose hydrogen and form more complex molecules in which boron atoms were linked by hydrogen bridges or co-ordinated with nitrogen in a second hydrazine molecule. This view is supported by the observation that when the initial product was hydrolysed and the hydrazine was estimated in the hydrolysate, the amount found corresponded closely to the total nitrogen content of the solid. Another indication that there was no cleavage of the N–N bond of hydrazine in this reaction is that no borazole was formed when the solid was heated to 180°. Three samples examined lost approximately one molecular proportion of hydrogen, leaving an involatile residue of the empirical formula $BN_{1{\cdot}12-1{\cdot}26}H_{2{\cdot}86-3{\cdot}08}$. Although there is no evidence on which to assign a structure to such a compound, its mode of formation is clearly different from that of borazole from the compound $NH_4(BH_3{\cdot}NH_2{\cdot}BH_3)$. The initial product had strong reducing properties, decolorizing permanganate instantaneously and precipitating silver from silver nitrate solution. It also exploded when heated in air or on treatment with concentrated sulphuric acid.

Experimental.—Diborane was prepared by the reduction of boron trichloride with lithium aluminium hydride (Finholt, Bond, and Schlesinger, *J. Amer. Chem. Soc.*, 1947, **69**, 1199). Hydrazine of 99·2% purity, as determined by Andrews's method, was prepared by distilling samples of material, which may have contained a little water, from barium oxide immediately before use. In a typical experiment diborane (11·8 millimoles) was distilled on to hydrazine (7·4 millimoles) in a trap attached to a vacuum system. Reaction was allowed to proceed at 0° for 30 hours, after which diborane (5·6 millimoles) and hydrogen (3·58 millimoles) were recovered. There was no residual hydrazine or other product volatile *in vacuo*. The purity of the hydrogen was checked by explosion in a Hempel pipette. These data give a ratio of N_2H_4 and B_2H_6 reacting to hydrogen formed of 1 : 0·84 : 0·48, corresponding to an empirical formula $BN_{1\cdot2}H_{4\cdot8}$ for the solid. The latter was also analysed (Found: B, 32·6, 30·4; H, 14·4; N, 52·0. Calc. for $BN_{1\cdot2}H_{4\cdot8}$: B, 33·4; H, 14·8; N, 51·8%). Data for a series of similar experiments are given below.

B_2H_6 taken (millimoles).	B_2H_6 recovered (millimoles).	N_2H_4 taken (millimoles).	H_2 formed (c.c.).	Ratio, $N_2H_4 : B_2H_6 : H_2$.
15·0	9·5	6·9	75	1 : 0·80 : 0·48
17·0	11·1	7·0	74	1 : 0·84 : 0·47
16·8	11·6	6·7	48·3	1 : 0·78 : 0·32
21·1	10·7	10·7	118	1 : 0·97 : 0·49
14·8	10·6	4·7	26·2	1 : 0·90 : 0·25

The product was insoluble in ether, benzene, acetone, chloroform, carbon tetrachloride, ethyl acetate, dimethylformamide, liquid ammonia, and hydrazine. With the last it reacted slowly, liberating hydrogen.

When samples of the solid product were heated in a vacuum in a sealed 100-c.c. bulb at 180—200° for 2—3 hours, hydrogen was evolved and subsequently identified by being sparked with air. There

were no other volatile products. The residue was a white solid, the nitrogen and hydrogen content of which was determined. The following are the results of three such experiments:

Composition of solid.	$BN_{1\cdot19}H_{4\cdot81}$	$BN_{1\cdot16}H_{4\cdot81}$	$BN_{1\cdot12}H_{4\cdot84}$
Wt. taken (g.)	0·345	0·361	0·150
Vol. of H_2/g. of solid (c.c.)	242	262	99·1
Moles of H_2/mole of solid	1·01	1·08	0·93
Composition of the residue.	$BN_{1\cdot19}H_{2\cdot80}$	$BN_{1\cdot16}H_{2\cdot81}$	$BN_{1\cdot12}H_{2\cdot88}$
N; H, % (calc.)	55; 9·2	56·5; 9·0	53; 10·5
N; H, % (found)	52; 9·0	55; 9·0	51·5; 10·4

Samples of the initial reaction product were hydrolysed with 3N-hydrochloric acid at room temperature in an apparatus similar to that used by Emeléus and Woolf (*J.*, 1950, 164). Hydrogen evolution was at first rapid but subsequently became very slow. The volume of hydrogen per g. of solid in three experiments was 195, 120, and 140 c.c. This lack of consistency is probably due to the formation in the hydrolysis of lower acids of boron which decompose slowly with liberation of hydrogen.

A further indication that such acids are formed was given by the difficulty of estimating hydrazine in the hydrolysate by Andrews's method. Samples of the solid were boiled with dilute hydrochloric acid, but, on titration with potassium iodate, the titre was greater than expected and the end point was not permanent. When, however, the hydrolysed solution was set aside in air for 2—3 days before titration, a fairly permanent end point was obtained. The nitrogen content of the solid, estimated as hydrazine from these titrations, corresponded fairly closely with the nitrogen content of the solid used (Found, for a solid of the composition $BN_{1\cdot03}H_{4\cdot5}$: N, 48·1. Calc. for $BN_{1\cdot03}H_{4\cdot5}$: N, 48·5%. Found, for a solid of the composition $BN_{1\cdot33}H_{5\cdot1}$: N, 53·0. Calc. for $BN_{1\cdot33}H_{5\cdot1}$: 54·0%). The two formulæ given above as representing the composition of the solid used are based on the ratio of diborane and hydrazine reacting.

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UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, October 27th*, 1950.]

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185. *Chromatographic Separation of Choline-containing Phospholipids from Phospholipid Mixtures.*

By T. H. BEVAN, G. I. GREGORY, T. MALKIN, and A. G. POOLE.

ONE of the major difficulties in the phospholipid field is the separation of the naturally occurring complex mixtures into their four main types (lecithin, kephalin, sphingomyelin, phosphatidyl serine). In the light of recent work (cf. Hutt *et al.*, *Nature*, 1950, **165**, 314) earlier methods based on solubility relations are no longer valid, and methods based on complex salt formation are tedious and wasteful. For these reasons we have explored the possibility of chromatographic separation, and we find, using the technique outlined below, that it is possible to separate the phospholipids containing choline (lecithin and sphingomyelin) from those containing ethanolamine and serine (kephalin and phosphatidyl serine).

Experimental.—Paper chromatograms. Uniform spots of a 10% chloroform solution of the crude phospholipid mixtures were placed on the starting line of Whatman No. 1 filter-paper sheets which were then hung from troughs contained in glass tanks as described by Consden, Martin, and Gordon (*Biochem. J.*, 1944, **38**, 224).

The solvent used was a ternary mixture from the water-poor phase obtained from chloroform (800 ml.), ethyl alcohol (200 ml.), and water (25 ml.). The chromatograms were run for 6 hours at 18°; the solvent front had then almost reached the bottom of the papers (≃ 14″ from the starting line), which were then removed and dried.

To detect the positions of the different phospholipids, the papers were divided longitudinally into two parts, which were treated as follows: (*a*) One was immersed in a 0·2% solution of ninhydrin in ethyl alcohol, removed, dried, and carefully heated before an electric fire. Blue or purple spots indicate the positions of the phospholipids containing ethanolamine and serine. (*b*) The other was treated with a 1% solution of phosphomolybdic acid in a mixture of equal volumes of ethyl alcohol and chloroform, washed in running water for 15—20 minutes, and dried. The position of the choline-containing phospholipids could be seen at this stage as faint yellow precipitates; on treatment with a 1% solution of stannous chloride in 3N-hydrochloric acid, well-defined blue spots appeared.

Lecithin obtained from ground nuts and egg yolk, by precipitation of the alcohol-soluble phospholipids with acetone, gave, respectively, three and four slow-moving fractions reacting with ninhydrin, but not with phosphomolybdic acid, of R_F values 0·02, 0·05, 0·20, and 0·02, 0·05, 0·17, and 0·28, together with a well-separated fraction reacting with phosphomolybdic acid, of R_F 0·90. Under the same conditions serine, choline, and ethanolamine gave R_F values of 0·01, 0·09, and 0·44 respectively.

Chromatograms of egg lecithin, purified by Pangbourne's improved cadmium chloride method

(*J. Biol. Chem.*, 1941, **137**, 545), which is regarded as the best method for the purification of lecithin, still showed the presence of ninhydrin-reactive material.

Saturated αα′- and αβ-phosphatidyl ethanolamines (kephalins) and αβ-dipalmityl phosphatidyl choline (lecithin), synthesised in this laboratory, have been chromatographed as above. The kephalins reacted with ninhydrin and had very low R_F values, whilst the lecithin reacted with phosphomolybdic acid and had R_F 0·97. This value was also found for a hydrogenated lecithin obtained from ground nuts.

A similar investigation carried out with a sphingolipid mixture obtained from beef brain by the method of Carter, Haines, Ledyard, and Norris (*J. Biol. Chem.*, 1947, **169**, 77) gave poorly separated ninhydrin-reactive fractions of low R_F values, and a well separated choline fraction of R_F 0·92.

Column separations (solvent as used for paper chromatograms). A column 40 cm. long and 4 cm. in diameter was packed with powdered cellulose as described by Hough, Jones, and Wadman (*J.*, 1949, 2511). The column was charged with a solution of 500 mg. of crude lecithin from ground nuts (as prepared above) in 5 ml. of solvent; this was washed on to the column with five successive 5-ml. portions of solvent. The solvent, supplied from a constant-head reservoir, was collected in 500-ml. portions. After removal of the solvent under reduced pressure, the solid residue was dissolved in 3—5 ml. of chloroform and poured into 10—15 ml. of acetone. The first two 500-ml. portions left no residue and were rejected; the third gave a copious precipitate (≃ 300 mg.), the fourth a small precipitate, and the fifth again left no residue.

Paper chromatograms of these materials showed complete absence of ninhydrin-reactive fractions. Chromatographic separation thus provides an efficient method of obtaining small samples of uncontaminated choline-containing phospholipids.

We thank Mr. D. A. Brown, who prepared our egg lecithin from commercial dried egg.

THE UNIVERSITY, BRISTOL. [*Received, November 15th*, 1950.]

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186. *The Purification of Brucine.*

By E. E. TURNER.

IN a recent note (*J.*, 1950, 2908) Kacser states that "in addition to pharmaceutical specifications, there are meagre and conflicting data on the specific rotation" of brucine, and refers, among other papers, to one by Jamison and Turner (*J.*, 1942, 437). In fact, these authors do not give a value for the specific rotation of brucine in their paper. Kacser then says that "chloroform solutions of brucine were observed to develop a pale brown colour when kept in daylight. The processes were faster under ultra-violet radiation." He ascribed the change to photochemical oxidation of the brucine, referring to results obtained by Leuchs and others (*Ber.*, 1937, **70**, 2369; 1940, **73**, 885) under very different experimental conditions. In fact, as is well known, pure chloroform is oxidised under the influence of light, giving carbonyl chloride, and our records show that chloroform, originally pure, which has been kept for some time frequently gives a brownish or even a brownish-red colour with brucine, owing to the presence of carbonyl chloride. It is hardly necessary to say that under the influence of ultra-violet radiation pure chloroform is very rapidly oxidised to carbonyl chloride.

Kacser then says that his commercial sample of brucine had $[\alpha]_{5461}^{20}$ −139·6° in chloroform and that after being extracted by cold, and crystallised from warm, toluene its rotation rose to −149·3°. In our experience, commercial brucine has a specific rotation up to about $[\alpha]_{5461}^{20}$ −145° in chloroform, corresponding to a partly dehydrated tetrahydrate. The pure tetrahydrate has, according to our records, $[\alpha]_{5461}^{20}$ −137·7° ± 0·5° and $[\alpha]_{5780}^{20}$ −117·3° ± 0·5°, in chloroform (*c*, 1·000 ± 0·1). This substance, or any hydrated brucine, would be dehydrated by Kacser's method of "purification," and azeotropic dehydration doubtless accounts for most, although possibly not for all, of his recorded rise in specific rotation. In our experience, if commercial hydrated brucine is once crystallised from water the resultant tetrahydrate is not very soluble in chloroform and a suspension of the air-dried material in this solvent appears to contain free water; addition of anhydrous sodium sulphate causes the brucine to dissolve and, if the solution is then poured into a large bulk of dry light petroleum (b. p. 40—60°), pure anhydrous brucine is precipitated having m. p. 178—179° (corr.), $[\alpha]_{5461}^{20}$ −149·9° ± 0·5°, $[\alpha]_{5780}^{20}$ −127·6° ± 0·5° in pure chloroform (*c* of the order 1·00—2·50).

Incidentally, if a dry solution of pure brucine in chloroform is treated with enough dry light petroleum to induce substantial crystallisation, the brucine crystallises with 1 mol. of chloroform as voluminous needles, having $[\alpha]_{5461}^{20}$ −115·8° ± 0·5° and $[\alpha]_{5780}^{20}$ −98·4° ± 0·5° in chloroform (*c* of order of 1·00). If this product is heated in a high vacuum at 120° to constant weight it gives pure anhydrous brucine, of m. p. 178—179° (corr.), $[\alpha]_{5461}^{20}$ −149·9° ± 0·5°, $[\alpha]_{5780}^{20}$ −127·6° ± 0·5° in chloroform (*c* of order of 1·00).

Kacser, although claiming to have obtained " definitive " constants, does not give any indication of experimental error in his values for [α], nor does he say what kind of polarimeter tube he used. Our own observations were made with all-glass " macro " 2-dm. tubes, with a Lowry spectro-polarimeter, solutions being made up using routine precision methods (pure chloroform; thermostatically-controlled temperature; N.P.L.-standardised measuring flasks; etc.).

Kacser apparently interprets the results of Hilditch (*J.*, 1908, **93**, 700) as " conflicting." What Hilditch found was that the specific rotation varied with concentration, which is not unusual. In our experience the specific rotation of pure anhydrous brucine in pure chloroform does not change significantly over the concentration range 1—2·5. [The specific rotation of brucine tetrahydrate cannot be determined for $c = 2·5$ in chloroform, since the solubility of the hydrate is too low. Qualitative observation (cf. above) suggests that the hydrate is partly dehydrated by chloroform at room temperatures.]

BEDFORD COLLEGE, LONDON. [*Received, December 1st*, 1950.]

187. 1-*Nitromethylcyclohexanol.*

By GEORGE A. R. KON.

IN the course of some synthetic work now in progress in these laboratories a quantity of 1-nitromethyl*cyclo*hexanol was required. This substance had originally been obtained by Fraser and Kon (*J.*, 1934, 604) in the course of an investigation on nitromethyl*cyclo*hexene and related nitro-olefins.

In a recent communication Nightingale, Erickson, and Knight (*J. Org. Chem.*, 1950, **15**, 782) state that they were unable to repeat this preparation, but describe a successful method which differs but little from that originally published. Hass and Riley (*Chem. Reviews*, 1943, **32**, 384) also say that the earlier work could not be repeated and quote the results obtained by Bourland and by Larrison, whose work is recorded in theses (Purdue University, 1941 and 1942, respectively) and is not directly accessible to us. A similar statement is contained in a preamble to U.S.P. 2,343,256 (Hass and Bourland) and U.S.P. 2,383,603 (Larrison and Hass); however, this would appear to refer to the formation of dinitroalkanes from ketones and nitromethane and not to the condensation of *cyclo*hexanone with nitromethane.

When this condensation was repeated exactly in accordance with the original directions the nitro-alcohol was obtained without difficulty, although the yield did not exceed 27% and is thus comparable with that quoted by Nightingale, Erickson, and Knight (*loc. cit.*) (26% when the reaction mixture was not heated). An improved yield (43%) results from keeping the mixture for 3 days and a further improvement (to 47%) is attained by increasing the amount of sodium ethoxide three-fold. However, a further increase in the amount of catalyst does not appear to be desirable; an equimolecular amount of sodium ethoxide affords a fair yield of condensation product, but this consists largely of the olefin, nitromethyl*cyclo*hexene (Found: C, 58·0; H, 8·2. Calc. for $C_7H_{11}O_2N$: C, 59·5; H, 7·9%), which is also the main product when piperidine is used as a catalyst. With sodium *iso*propoxide the yields are somewhat lower than with the ethoxide and lower still (33%) with the methoxide.

Experimental.—The optimum conditions for the condensation appear to be the following: a solution of 0·5 g. of sodium in 15 c.c. of ethanol is added to a mixture of 12·2 g. of nitromethane and 19·6 g. of *cyclo*hexanone (0·2 mole of each) and the whole kept at room temperature for 3 days. Water and 2N-sulphuric acid are added, the oil extracted with ether, and the extract shaken with water, 2N-sodium hydrogen carbonate, and again with water. The solvent is removed from the dried (Na_2SO_4) solution and the residue distilled from a flask with a short Vigreux column. The yield of material, b. p. 125—127°/17 mm., is 12 g. (47%) (Found: N, 9·1. Calc. for $C_7H_{13}O_3N$: N, 8·8%).

In all the above experiments carefully purified materials were used; in particular, the nitromethane was shaken with 2N-sodium hydrogen carbonate, dried, and redistilled. When a commercial specimen of nitromethane was used without purification the yield of nitro-alcohol was halved and this may well be an important factor; on the other hand, there appears to be no advantage in warming the reaction mixture to 50° and using the stronger solution of catalyst recommended by Nightingale *et al.* (*loc. cit.*), or in the precautions used by them in preparing it (these do not, in any case, differ significantly from the standard textbook procedure). Nevertheless, it must be admitted that the original yield of 45% is not always attained and we are at present unable to account for this discrepancy.

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188. 7-*Ethyl*-2-*methylnaphthalene*, 7-*Ethyl*-1 : 2-*dimethylnaphthalene*, *and* 6-*Ethyl*-1 : 4-*dimethylnaphthalene*.

By Wesley Cocker and Donal H. Hayes.

In the course of a wider investigation it became necessary, for comparative purposes, to synthesise the substituted naphthalenes mentioned in the title. 6-Ethyl-1 : 4-dimethylnaphthalene has previously been obtained from santinic acid by heating it with barium oxide (Gucci and Grassi-Cristaldi, *Gazzetta*, 1892, **22**, I, 41) and by synthesis from 4-ethylacetophenone (Ruzicka and Eichenberger, *Helv. Chim. Acta*, 1930, **13**, 1117, 1123).

7-Ethyl-2-methyl- and 7-ethyl-1 : 2-dimethyl-naphthalene, which are new, were obtained as follows. Methylsuccinic anhydride was condensed with ethylbenzene to yield β-*p*-ethylbenzoyl-*iso*butyric acid (cf. Cocker *et al.*, *Chem. and Ind.*, 1949, 641, for earlier refs.; *J.*, 1950, 1781). Its identity was established by an unambiguous synthesis. ω-Chloro-4-ethylacetophenone (Auwers, *Ber.*, 1906, **39**, 3759) with ethyl methylmalonate gave an ester which, on hydrolysis and heating above its melting point, yielded β-*p*-ethylbenzoyl*iso*butyric acid. This was reduced to the corresponding butyric acid which was cyclised to 7-ethyl-1 : 2 : 3 : 4-tetrahydro-1-keto-2-methylnaphthalene. Reduction, followed by dehydrogenation, gave 7-ethyl-2-methylnaphthalene, and reaction of the tetralone with methylmagnesium iodide gave a product which when dehydrogenated yielded 7-ethyl-1 : 2-dimethylnaphthalene.

6-Ethyl-1 : 4-dimethylnaphthalene was obtained by condensation of *p*-xylene with ethylsuccinic anhydride which gave β-(2 : 5-dimethylbenzoyl)-α-ethylpropionic acid as the main product. This was converted into the desired naphthalene by conventional methods.

7-*Ethyl*-2-*methylnaphthalene*.—β-p-*Ethylbenzoyl*isobutyric *acid*. A solution of ethylbenzene (10 g.) and methylsuccinic anhydride (10 g.), in nitrobenzene (150 c.c.), was treated with aluminium chloride (25 g.), in nitrobenzene (50 c.c.), and the mixture was set aside overnight. After decomposition with ice and hydrochloric acid, the nitrobenzene layer was separated, washed with water, and extracted several times with ammonia. The extract was distilled in steam and acidified, yielding a solid (15 g.; m. p. 87—95°). It was crystallised thrice from dilute alcohol from which the required *keto-acid* (10 g.) was obtained as fine needles, m. p. 108—109° (Found : C, 71·0; H, 7·3. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%). Its *semicarbazone* crystallised from dilute alcohol as needles, m. p. 186° (Found : C, 60·3; H, 6·7. $C_{14}H_{19}O_3N_3$ requires C, 60·6; H, 6·9%).

α-*Carboxy*-β-p-*ethylbenzoyl*isobutyric *acid*. ω-Chloro-4-ethylacetophenone (7·5 g.), in dry ether (50 c.c.), was slowly added to the sodio-derivative of ethyl methylmalonate [from this ester (7·2 g.) and sodium (0·95 g.)], in ether (100 c.c.). The mixture was stirred and refluxed for 4 hours. Water was added, and the ethereal layer separated, dried, and distilled. The fraction (1·6 g.), b. p. 210—212°/11 mm., consisted of the required ester. This was hydrolysed with excess of 10% methanolic potassium hydroxide and yielded the required *acid* (1·1 g.), m. p. 164—167° (decomp.), which separated from methyl alcohol as micro-needles, m. p. 167—168° (decomp.) (Found : *M*, 270. $C_{14}H_{18}O_5$ requires *M*, 264).

β-p-*Ethylbenzoyl*isobutyric *acid*. The preceding compound (0·75 g.) was heated at 180° for 10 minutes and the product crystallised from dilute alcohol. It then gave m. p. 107°, undepressed by a sample prepared by the alternative method described above.

γ-p-*Ethylphenyl*-α-*methylbutyric acid*, obtained (4·7 g.) from the above keto-acid (10 g.), distilled at 193—194°/5 mm. (Found : C, 75·9; H, 8·6. $C_{13}H_{18}O_2$ requires C, 75·7; H, 8·7%). Its acid chloride, obtained by treatment of the acid (4·3 g.) with thionyl chloride (2·2 c.c.) overnight at room temperature, followed by refluxing for 30 minutes, distilled at 170—175°/20 mm.

7-*Ethyl*-1 : 2 : 3 : 4-*tetrahydro*-1-*keto*-2-*methylnaphthalene*. The acid chloride (3·5 g.) in carbon disulphide (100 c.c.) was treated with aluminium chloride (2·3 g.) added in one portion. The mixture was refluxed for 10 minutes, cooled, decomposed with ice and hydrochloric acid, and distilled in steam. The distillate yielded an oily *ketone* (3 g.), b. p. 166—167°/20 mm. (Found : C, 82·7; H, 8·25. $C_{13}H_{16}O$ requires C, 83·0; H, 8·5%). Its *semicarbazone* (colourless prisms) had m. p. 217—219·5° (Found : C, 68·5; H, 7·8. $C_{14}H_{19}ON_3$ requires C, 68·6; H, 7·8%).

7-*Ethyl*-1 : 2 : 3 : 4-*tetrahydro*-2-*methylnaphthalene* was obtained as an oil (0·8 g.; b. p. 128—132°/15 mm.) by the reduction of the above tetralone (1·5 g.) (Found : C, 88·5; H, 11·1. $C_{13}H_{18}$ requires C, 89·6; H, 10·4%).

7-*Ethyl*-2-*methylnaphthalene*. The tetralin (0·7 g.) was heated with selenium (2·1 g.) for 2·5 hours at 335—340°. The product (b. p. 125—128°/10 mm.) was distilled from sodium and converted into its picrate from which the pure *naphthalene* was regenerated, b. p. 135—140°/15—20 mm. (Found : C, 91·2; H, 8·4. $C_{13}H_{14}$ requires C, 91·8; H, 8·2%). Light absorption : Max., <2300, 2740 (2910), 3170, and 3200 A.; log ε = ?, 3·63 (2·37), 2·30, and 2·30, respectively. Its *picrate* crystallised from methyl alcohol as bright yellow needles, m. p. 85—85·5° (Found : C, 56·5; H, 4·3. $C_{19}H_{17}O_7N_3$ requires C, 57·1; H, 4·3%).

7-*Ethyl*-1 : 2-*dimethylnaphthalene*.—7-*Ethyl*-3 : 4-*dihydro*-1 : 2-*dimethylnaphthalene*. The above tetralone (2·5 g.) in dry ether (30 c.c.) was slowly added to a stirred, boiling solution of methylmagnesium

iodide (from magnesium, 1 g.). The mixture was refluxed for 1 hour, cooled, and decomposed with ice and sulphuric acid. The ethereal layer yielded an oil (3 g.; b. p. 140—147°/17 mm.), which was heated for 1 hour at 160° with potassium hydrogen sulphate (7·6 g.). The oily *dihydro*-compound (2·2 g.) distilled at 149—154°/18 mm. It did not give a satisfactory analysis (Found: C, 87·0; H, 8·9. $C_{14}H_{18}$ requires C, 90·3; H, 9·7%).

7-*Ethyl*-1 : 2-*dimethylnaphthalene*. The previous compound (2 g.) was heated with selenium (6 g.) at 335—340° for 2·5 hours and yielded a *hydrocarbon* (1·1 g.), which was purified through its picrate and then distilled at 133—135°/10 mm. (Found: C, 91·2; H, 8·8. $C_{14}H_{16}$ requires C, 91·3; H, 8·7%). Light absorption: Max., <2300(2700), 2810, and 3190 A.; log ε = ? (3·61), 3·69, and 2·43 respectively. Its *picrate* crystallised from methyl alcohol as orange needles, m. p. 104—105° (Found: C, 58·1; H, 4·7. $C_{20}H_{19}O_7N_3$ requires C, 58·1; H, 4·6%). Its *trinitrotoluene* adduct crystallised from methyl alcohol as lemon-yellow needles, m. p. 88—89° (Found: C, 61·3; H, 5·2. $C_{31}H_{31}O_6N_3$ requires C, 61·3; H, 5·1%).

6-*Ethyl*-1 : 4-*dimethylnaphthalene*.—β-(2 : 5-*Dimethylbenzoyl*)-α-*ethylpropionic acid*. Ethylsuccinic anhydride (11 g.) was condensed, at room temperature, with *p*-xylene (11 g.), in nitrobenzene (100 c.c.) using aluminium chloride (26 g.) in nitrobenzene (75 c.c.). The *product* (13 g.) was a yellow solid, m. p. 81—85°, which separated from dilute alcohol as flat prisms, m. p. 100—102° (Found: C, 71·5; H, 7·5. $C_{14}H_{18}O_3$ requires C, 71·8; H, 7·7%). Its *semicarbazone* separated from alcohol as prisms, m. p. 164—165° (Found: C, 62·6; H, 7·4. $C_{15}H_{21}O_3N_3$ requires C, 61·9; H, 7·2%).

γ-(2 : 5-*Dimethylphenyl*)-α-*ethylbutyric acid* (7·6 g.) was obtained from the previous compound (8·4 g.) as a colourless oil, b. p. 195—197°/15 mm. (Found: C, 76·1; H, 9·2. $C_{14}H_{20}O_2$ requires C, 76·4; H, 9·1%). Its acid chloride distilled at 163—166°/10 mm.

2-*Ethyl*-1 : 2 : 3 : 4-*tetrahydro*-1-*keto*-5 : 8-*dimethylnaphthalene* (3·5 g.) was obtained from the acid chloride (4·1 g.) in carbon disulphide (250 c.c.), by cyclisation with aluminium chloride (2·7 g.). The reaction was completed by heating for 10 minutes and the *tetralone* was collected at 267—270°/16 mm. (Found: C, 82·7; H, 8·8. $C_{14}H_{18}O$ requires C, 83·2; H, 8·9%). It failed to yield a semicarbazone.

2-*Ethyl*-1 : 2 : 3 : 4-*tetrahydro*-5 : 8-*dimethylnaphthalene* (2·4 g.) was obtained from the tetralone (2·7 g.). It was collected at 146—147°/10 mm. (Found: C, 89·0; H, 10·7. $C_{14}H_{20}$ requires C, 89·4; H, 10·6%).

6-*Ethyl*-1 : 4-*dimethylnaphthalene*. The tetrahydro-compound (1·7 g.), heated with selenium (3·1 g.) for 2·5 hours at 335—340°, gave an oil (1·5 g.) which, when purified through its picrate, distilled at 158—161°/21 mm. Light absorption: Max., <2300, 2880, and 3250 A.; log ε = ?, 3·54, and 2·49 respectively. The m. p. of the picrate (red needles from methanol) remained steady at 80° (cf. Ruzicka and Eichenberger, *loc. cit.*, who give m. p. 85°). Its trinitrobenzene and trinitrotoluene adducts dissociated on attempted crystallisation.

TRINITY COLLEGE, DUBLIN. [*Received, December 22nd*, 1950.]

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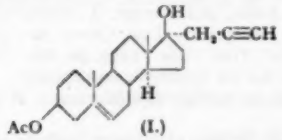
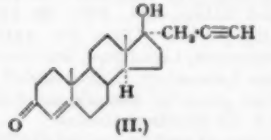
189. *The Preparation of 17α-Propargyltestosterone.*

By D. MAGRATH, V. PETROW, and R. ROYER.

DEHYDROEPIANDROSTERONE failed to react with propargyl bromide under the usual conditions of the Reformatsky reaction, and the addition of mercuric chloride or copper bronze to the reaction mixture proved of no avail. On replacement of propargyl bromide by the iodide, however, reaction occurred to give 3β-acetoxy-17α-propargylandrost-5-en-17β-ol (I) in 21% yield. Hydrolysis gave the corresponding 3β-hydroxy-compound, oxidised by the Oppenauer method to 17α-propargyltestosterone (II).



(I.)



(II.)

Dr. S. W. F. Underhill and Mr. W. S. Parr (Physiological Department, The British Drug Houses, Ltd.) have kindly examined (I) and (II) for biological activity with the following results:

	(I.)	(II.)
Androgenic activity	0	0
Œstrogenic activity, i.u./mg.	1·0	0
Progestational activity, i.u./mg.	0·002	0·004

The low biological activity of (II) is somewhat surprising as 17α-ethynyltestosterone—of which (II) is the homo-derivative—has about one-third of the activity of progesterone on subcutaneous

injection (cf. Inhoffen, Logemann, Hohlweg, and Serini, *Ber.*, 1938, **71**, 1024), whilst 17α-ethyltestosterone has about one-fifth of the androgenic activity of testosterone (Ruzicka, Goldberg, and Rosenberg, *Helv. Chim. Acta*, 1935, **18**, 1487).

Experimental.—Microanalyses are by Drs. Weiler and Strauss, Oxford. M. p.s are uncorrected. Optical rotations were measured in chloroform solution in a 2-dm. tube.

3β-*Acetoxy*-17α-*propargylandrost*-5-*en*-17β-*ol* (I). A solution of dehydro*epi*androsterone acetate (20 g.) in a mixture of dry benzene (40 ml.) and propargyl iodide (20·1 g.) was added slowly under anhydrous conditions to a stirred mixture of activated zinc dust (40 g. of sludge in benzene) in benzene (40 ml.), maintained under reflux. Reaction was completed by heating the whole for a further 30 minutes, whereafter the mixture was cooled, decomposed with ice-cold 2N-hydrochloric acid (400 ml.), and extracted with ether. The product (21·4 g.) in benzene solution was filtered through alumina (50 g.; B.D.H.), evaporation of the combined benzene eluates followed by crystallisation from methanol and finally acetone yielding 3β-*acetoxy*-17α-*propargylandrost*-5-*en*-17β-*ol* as needles, m. p. 149° (Found: C, 77·8; H, 9·3. $C_{24}H_{34}O_3$ requires C, 77·8; H, 9·3%).

17α-*Propargylandrost*-5-*en*-3β : 17β-*diol*, obtained by hydrolysis of the foregoing compound with alcoholic potash, formed needles (from benzene), m. p. 153—155°, $[\alpha]_D^{23}$ −91·0° (*c*, 0·382) (Found: C, 80·6; H, 10·0. $C_{22}H_{32}O_2$ requires C, 80·4; H, 9·8%).

17α-*Propargyltestosterone* (II).—A mixture of the foregoing compound (1·8 g.), aluminium *iso*propoxide (7·2 ml. of a 25% solution in toluene), toluene (33 ml.), and *cyclo*hexanone (19·2 ml.), was heated under reflux for 1½ hours. The cooled mixture was added to ice and 5N-hydrochloric acid (75 ml.), and the product extracted with ether. Treatment with light petroleum (200 ml.; b. p. 40—60°), followed by storage at 0°, gave a solid product (1·24 g.) which was repeatedly crystallised from aqueous methanol. 17α-*Propargyltestosterone* formed flakes (48%), m. p. 136—137°, $[\alpha]_D^{23}$ +57·3° (*c*, 0·417) (Found: C, 81·2; H, 9·4. $C_{22}H_{30}O_2$ requires C, 80·9; H, 9·3%).

The authors thank the Directors of The British Drug Houses for permission to publish these results.

CHEMICAL RESEARCH LABORATORIES, THE BRITISH DRUG HOUSES, LTD.,
LONDON, N.1. [*Received, December 22nd*, 1950.]

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190. *The Reduction of Aromatic Hydrocarbons with Lithium Aluminium Hydride.*

By ISAAC GOODMAN.

THE sole claim to the reduction of the aromatic nucleus by means of lithium aluminium hydride appears to be that by Sampey and Cox (*J. Amer. Chem. Soc.*, 1949, **71**, 1507) to have prepared tetrahydroanthracene and dihydrophenanthrene from anthracene and phenanthrene, respectively, at elevated temperatures (cf. Johnson, *Ann. Reports*, 1949, **46**, 143, where, however, a clerical error occurs).

The American authors, however, state that their tetrahydroanthracene was identified by a mixed melting point with "a sample prepared by reduction of anthracene with Raney nickel (m. p. 103—104°)," whilst "the dihydrophenanthrene and its picrate were identical with those prepared by Schmidt (*Ber.*, 1907, **40**, 4240)." These identifications are, however, known from other work to be unsatisfactory (cf. Schmidt *et al.*, *Ber.*, 1908, **41**, 4225; Schroeter, Müller, and Huang, *Ber.*, 1929, **62**, 645; Burger and Mosettig, *J. Amer. Chem. Soc.*, 1935, **57**, 2731; Durland and Adkins, *ibid.*, 1937, **59**, 138; Hall, Lesslie, and Turner, *J.*, 1950, 711; Garlock and Mosettig, *J. Amer. Chem. Soc.*, 1945, **67**, 2255; Kagehira, *Bull. Chem. Soc. Japan*, 1931, **6**, 241; Waterman, Leendertse, and Cranendonk, *Rec. Trav. chim.*, 1939, **58**, 83). In extensive work in this Laboratory, Raney nickel has never led to tetrahydroanthracene. Whilst the melting point given by Sampey and Cox is correct for tetrahydroanthracene, it is also close to that of 9 : 10-dihydroanthracene.

The reaction of anthracene and phenanthrene with lithium aluminium hydride has therefore been re-examined. The product from anthracene was obtained in substantially the yield and with the properties recorded by Sampey and Cox. Comparison with authentic samples showed it to be 9 : 10-dihydroanthracene and its characterisation was completed by oxidation to anthraquinone in conditions found by Schroeter (*Ber.*, 1924, **57**, 2003) to yield tetrahydroanthraquinone from tetrahydroanthracene, and anthraquinone from the dihydro-compound. The product from the reaction with phenanthrene was almost entirely unchanged hydrocarbon.

It is interesting that Sampey and Cox (*loc. cit.*) noted that neither naphthalene nor anthracene was reduced by the reagent in dioxan or ether. Indeed, the reaction with anthracene occurs only at a temperature above that at which lithium aluminium hydride decomposes and at

which phenanthrene was not attacked. There is therefore no evidence that a truly aromatic (benzenoid) nucleus has ever been reduced by this reagent. The reaction in the case of anthracene is associated with its meso-reactivity, and leads to a stable product with two benzenoid rings.

Experimental.—The conditions employed were substantially identical with those used by Sampey and Cox (*loc. cit.*). The pure hydrocarbons (9 g.) and the powdered reagent (8 g.) were heated at 220—230° for 6 hours in a nitrogen atmosphere, with continuous stirring by a steel paddle stirrer. In each case, a very vigorous reaction set in at about 210°, but shortly subsided. This was found to occur with the reagent alone, and corresponds to the exothermic decomposition of the latter. The cooled reaction mixtures were decomposed cautiously by water. The hydrocarbon products were isolated by repeated extraction with toluene (anthracene experiment) and with ethanol (phenanthrene experiment). The inorganic residues were then treated with acid to liberate remaining traces of hydrocarbon, which in the case of anthracene were accompanied by a small amount of carbonaceous material. The various hydrocarbon extracts were then combined and examined as follows.

Phenanthrene. Fractional crystallisation yielded three crops (7·14 g., in all), identified in each case as phenanthrene. The remaining alcoholic solution gave an orange-coloured picrate (0·8 g.), m. p. 142—144°, consisting of slightly impure phenanthrene picrate (equiv. to 0·35 g. of hydrocarbon). The total recovery of phenanthrene was thus 7·49 g. (83%). The mother-liquor from the picrate was treated with alkali and yielded a small hydrocarbon residue (0·17 g.) which was mainly oily, with a trace of crystalline component. The refractive index of the oil (n_D^{20} 1·6115) is lower than that recorded for dihydrophenanthrene (Burger and Mosettig, *loc. cit.*; Durland and Adkins, *J. Amer. Chem. Soc.*, 1938, **60**, 1501) so that formation of this hydrocarbon does not occur. Phenanthrene comprised 97·7% of the total recovered hydrocarbon.

Anthracene. Partial evaporation of the toluene solution gave two crops of crystals (total wt., 3·63 g.) identified as anthracene; the second crop was accompanied by traces of some orange-yellow crystals which were mechanically separated and had m. p. 254—258°. (This material did not yield a picrate in alcohol solution, and was not decolorised by maleic anhydride in xylene; it has not been further examined). The remaining toluene solution was evaporated to dryness, yielding a buff-coloured solid (4·63 g.) of m. p. 88—100°. The total hydrocarbon recovery was therefore 8·26 g. (91·8%), of which 43·9% was anthracene. Sampey and Cox claimed a 60% yield of tetrahydroanthracene in these conditions.

Crystallisation of the lower-melting reaction product from ethanol gave two fractions (2·7 and 0·75 g., respectively). Fraction A occurred as pale slightly yellow needles, m. p. 104—106°, not affected by recrystallisation. Fraction B had m. p. 103—105°. The crystal form of these materials differed from that of tetrahydroanthracene, and both depressed the m. p. on admixture with a synthetic specimen of the tetrahydro-compound. Both fractions resembled 9 : 10-dihydroanthracene, however, and did not depress the m. p. of an authentic sample (m. p. 107°) obtained by copper chromite-catalysed hydrogenation of anthracene (Burger and Mosettig, *loc. cit.*).

Fraction A (or B) (0·5 g. each) in acetic acid (4 c.c.) was treated with chromium trioxide (1·25 g.) in acetic acid (4 c.c.) and water (1 c.c.) with cooling. After 15 hours, the crystalline products were filtered off and washed with alcohol. Fraction A gave anthraquinone (0·5 g.), m. p. 278°, as sole product; fraction B gave the same quinone (0·48 g.), m. p. 266—270°, and dilution of the mother-liquors gave a further 0·09 g. of quinone, m. p. 160—220°. It thus appeared that fraction B might contain a trace of material other than 9 : 10-dihydroanthracene. This is not tetrahydroanthracene, however, for neither fraction B nor its yellow alcoholic mother-liquors gave derivatives with either picric acid or trinitrobenzene.

The author is indebted to Dr. E. T. Borrows for a discussion.

PETROCARBON, LTD., RESEARCH LABORATORIES,
TWINING ROAD, MANCHESTER, 17. [*Received, November 24th*, 1950.]

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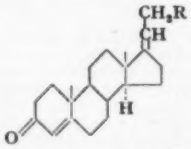
191. *Pregna*-4 : 16 : 20-*trien*-3-*one*.

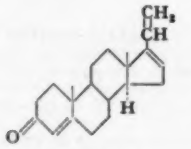
By J. K. NORYMBERSKI.

DURING preparation of 3-ketopregna-4 : 17-dien-21-yl acetate (I; R = OAc) by allylic rearrangement of 17α-vinyltestosterone with phosphorus tribromide and subsequent treatment of the crude bromide (I; R = Br) with potassium acetate in boiling acetone (Ruzicka and Müller, *Helv. Chim. Acta*, 1939, **22**, 416), formation of a by-product, m. p. 140—141°, was repeatedly observed. The same compound was formed from pure 3-ketopregna-4 : 17-dien-21-yl bromide (I; R = Br) under identical conditions; however, if the reaction was carried out at room temperature the by-product was not formed. The by-product analysed as $C_{21}H_{28}O$ and exhibited an absorption maximum at 238 mμ. (ε = 31,500), obviously to be explained by superposition of the band of a 4 : 5-unsaturated 3-ketone on that of a system of

conjugated double bonds. The presence of conjugated double bonds was supported by formation of a maleic anhydride adduct. These results strongly suggest that the compound is pregna-4 : 16 : 20-trien-3-one (II).

(I.)





(II.)

Reich (*Helv. Chim. Acta*, 1940, **23**, 219) reported the isolation of a compound, m. p. 124—135°, from the pyrolysis of 3-ketopregna-4 : 17-dien-21-yl pyridinium bromide (I; R = Br{NC_5H_5}) and, without further characterisation, proposed for it, formula (II). This work was repeated and the product of pyrolysis found to be identical with the " trienone " obtained from 3-ketopregna-4 : 17-dien-21-yl bromide (I; R = Br) and potassium acetate.

Experimental.—Microanalyses by Drs. Weiler and Strauss, Oxford.

Treatment of 3-*ketopregna*-4 : 17-*dien*-21-*yl bromide with potassium acetate.* (*a*) Crude 3-ketopregna-4 : 17-dien-17-yl bromide, prepared from 17α-vinyltestosterone (1·2 g.) by Ruzicka and Müller's procedure (*loc. cit.*), was heated in acetone (20 c.c.) with anhydrous potassium acetate (3·0 g.) and potassium iodide (trace) under reflux for 2 hours. After cooling, the mixture was diluted with ether (20 c.c.), the potassium salts were removed by filtration, and the filtrate was freed from solvents. The residue (1·3 g.) gave, on crystallisation from hexane, 3-ketopregna-4 : 17-dien-21-yl acetate (0·70 g.), m. p. 85—93°; recrystallisation from aqueous methanol raised the m. p. to 105—106°. Chromatography of the mother-liquors on neutral alumina gave a further quantity (0·29 g.) of the same product (fractions 5—7, benzene–light petroleum, 1 : 1, and benzene). Fractions 3 and 4 (0·16 g.) eluted with benzene–light petroleum (1 : 1) gave, on crystallisation from methanol, pregna-4 : 16 : 20-trien-3-one in long needles, m. p. 140—141°, undepressed on admixture with the trienone, m. p. 137—140°, prepared by Reich's procedure (*loc. cit.*), $[\alpha]_D$ +147° (*c*, 0·754, in chloroform). Light absorption (in ethanol): Max. 238 mμ.; ε = 31,500 (Found: C, 84·9; H, 9·6. Calc. for $C_{21}H_{28}O$: C, 85·1; H, 9·5%).

(*b*) The pure bromide (2·0 g.; m. p. 126—127°) was treated as under (*a*) with potassium acetate (3·0 g.) and potassium iodide (trace) in boiling acetone (70 c.c.). The crude reaction product gave, on repeated crystallisation from aqueous methanol, needles (0·27 g.), m. p. 137—140°, identical with the " trienone " from (*a*). The normal product, 3-ketopregna-4 : 17-dien-21-yl acetate (0·90 g.), was obtained from the mother-liquors.

(*c*) The pure bromide (2·0 g.) was shaken with anhydrous potassium acetate (3·0 g.) and potassium iodide (trace) in acetone (70 c.c.) for 20 hours at 18°. Crystallisation of the crude reaction product from hexane and then from aqueous methanol gave the acetate (0·77 g.), m. p. 102—104°. Chromatography of the mother-liquors on neutral alumina gave only further quantities of the same product.

Maleic anhydride adduct.—The foregoing " trienone " (0·225 g.) was heated in dry, thiophen-free benzene (2 c.c.) with maleic anhydride (0·075 g.) for 4 hours under reflux. After 3 days at 17—20° the *adduct* (0·15 g.) was collected; it crystallised from ethyl acetate in colourless needles, m. p. 241—243° (*in vacuo*) (Found: C, 75·8; H, 7·5. $C_{25}H_{30}O_4$ requires C, 76·1; H, 7·6%).

The author thanks the Directors of British Schering Research Laboratories Limited for permission to publish this work, and Dr. J. S. H. Davies for his interest in it.

British Schering Research Institute,
Alderley Edge, Cheshire.

[*Received, November* 30*th*, 1950.]

FREDERIC STANLEY KIPPING

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[*To face p.* 849.

OBITUARY NOTICE.

FREDERIC STANLEY KIPPING.*

1863—1949.

FREDERIC STANLEY KIPPING was born on August 16th, 1863, at Higher Broughton, Manchester. He was the eldest son of James Stanley and Julia Kipping and had two brothers and four sisters. His father held a post in the Manchester branch of the Bank of England of which his paternal grandfather was head. His grandfather on his mother's side was C. A. Duval, a Manchester artist of considerable reputation.

Kipping early acquired that interest in open-air life which was never to leave him. His father owned a small farm near Higher Broughton, which was at that time practically in the open country. Here he made himself generally useful and gained a fair knowledge of animals and practical agriculture. In the early days the Kipping children had a governess but at the age of eleven Frederic Stanley entered Manchester Grammar School on the same day as Herbert Brereton Baker. It is remarkable that both these boys became Longstaff Medallists of the Chemical Society. He had already become interested in chemistry through his father's friend and neighbour, J. Carter Bell, the public analyst for Cheshire, who showed him various simple precipitation reactions in inorganic chemistry, and advised his father to make him an analytical chemist. No doubt at this time that honourable profession was still generally regarded from the Dickensian point of view, so clearly indicated in "Our Mutual Friend."

Kipping remarks that the practical chemistry at Manchester Grammar School consisted almost entirely of qualitative analysis but unaccompanied by any clear explanation of its principles. During the holidays he assisted Mr. Carter Bell with the ordinary routine analysis of water, milk, and other foodstuffs. He also spent a year at the Lycée de Caen where food and sanitary arrangements were vile but the teaching of Latin was specially good. Kipping matriculated at the University of London in 1879 in the First Division and thereupon entered Owens College, Manchester, his family having meanwhile removed to Platt Abbey, a house familiar to this day to all those who travel on a 42 'bus along the Palatine Road to the Burlington Street laboratories. After three years, in which he studied mathematics, physics, botany, chemistry, and zoology, he graduated B.Sc. (London) with Second Class Honours in Zoology. He found Miles Marshall, the professor of Zoology, an excellent and inspiring teacher and Roscoe extremely kind and interested in his students. Schorlemmer, who was the first Professor of Organic Chemistry in this country, did not attract him however—his lectures were read without emphasis or pause from notes held close to the nose. After a short experience of this mode of presentation of organic chemistry Kipping devoted Schorlemmer's lecture hours to the practice of billiards in an adjacent hotel, thus acquiring a facility which he never lost. On the whole, with the exception of zoology, he found college work dull and unsatisfactory, but he used the fives courts a good deal and played cricket and lacrosse.

After graduation as an External student of the University of London in 1882 he obtained a post as chemist to the Manchester Gas Department in Rochdale Road and later at Gaythorne Street. The duties of the post, except for occasional work throughout the night, were not heavy but afforded him very useful and varied analytical experience which, at the age of 19, may have laid the foundation of the scrupulous care and accuracy of his research work. He had plenty of time for reading and was frequently able to leave the laboratory at 4.30—5.0 p.m. to catch a train on the former M.S.J. and A. Railway to Old Trafford in order to play tennis at the Northern Lawn Tennis Club. Here and on many other grounds he played in matches against the leading clubs of Lancashire and adjoining counties. He remained in the service of the Corporation for about three years to the age of 23. Until then he seems to have shown no particular signs of devotion to chemistry although he was doubtless maturing. About this time, however, a friend of his family, Dr. Adolf Liebman, a chemist at Levinstein's, Blackley, strongly advised a period of study in Germany and pointed out the lack of opportunity for advancement in Kipping's post at the gas works.

Following this advice, he entered the University of Munich in the Spring of 1886 and was there given a bench in one of the organic laboratories which was supervised by W. H. Perkin, jun., who had entered von Baeyer's Institute in 1882. There he carried out various organic preparations and after some months commenced research under Perkin's guidance on the

* Abridged, by permission, from *Obituary Notices of Fellows of the Royal Society*, Vol. 7.

synthesis of closed carbon chains. Thus began a scientific association which was to last until the death of Perkin in 1926 and was destined to influence the lives of both men, not only on the scientific but also on the personal side. Late in 1886 Perkin returned to England and thenceforward Kipping continued his research unaided except for the written advice which Perkin sent him from time to time. At that time Claisen, Bamberger, and von Pechmann were Privat-dozenten and Nef was a student. Work in the laboratory began at 8 and continued till 6 or after, with a rather long interval for Mittagessen—and chess. There was much skating in the winter. Kipping saw very little of von Baeyer. He refers to one occasion, however, on which he showed him with some pride a product he had isolated. The Geheimrath looked at it under a lens, snapped out " Ach, Harz " and stalked away ! This may have been the origin of Kipping's critical and, to say the least, realistic attitude to his students' laboratory efforts. However, he took his Ph.D. degree *summa cum laude*, after which he returned to England and for a short time assisted his father, who had turned his attention to chemical manufacturing on the small scale. The preparations of sulphur chloride and of carbolic disinfecting powder in the stables of Platt Abbey were not very congenial or successful ventures and did not last very long.

In the autumn of 1887, T. E. Thorpe and Emerson Reynolds as Examiners for the University of London awarded Kipping the degree of D.Sc. He was the first candidate on whom this degree was conferred on the grounds of research. It would appear, however, that his Munich work sufficed for both his Doctorates, a happy state of affairs which would not now commend itself to Faculties of Science. Immediately afterwards he was offered the post of demonstrator under W. H. Perkin, jun., who had by now been appointed Professor of Chemistry at the Heriot-Watt College in Edinburgh. The remuneration was £20 a year " with prospects." Most of the teaching was done in the evening but Kipping was usually on duty for most of the day, spending much time in research, again under Perkin's direction. In March 1888 he married his cousin, Lily Holland, the daughter of W. T. Holland, J.P., of Bridgwater and grand-daughter of C. A. Duval. During their engagement Perkin met his future wife, Miss Holland's elder sister, at the house of Kipping's parents.

During the Edinburgh period the writing of the famous " Organic Chemistry " (always known as " Perkin and Kipping ") was begun. This work was one of the earliest text-books on the subject and was first published in 1894. It has enjoyed an enormous reputation and has passed through many editions, the latest of which (1949) presents an excellent picture of the present-day position of the science. After about a year at the Edinburgh College Kipping was made Assistant Professor of Chemistry and Lecturer in Agricultural Chemistry at a total remuneration of £150 a year.

In late 1890 an event occurred which greatly influenced his future work and afforded him many stimulating contacts and the opportunity of directing the research of beginners. H. E. Armstrong, to Kipping's " astonishment and satisfaction," offered him the post of chief demonstrator in the Chemistry Department at the Central Technical College of the City and Guilds of London Institute at £240 a year. (The College is now incorporated in the Imperial College of Science and Technology, and the Chemistry Department closed. Many will remember the heated discussion which took place about 1910 regarding the wisdom of this step, Armstrong having built up a most flourishing school of research.) Kipping accepted this offer " with alacrity " and he and his wife removed from Graham Street, Edinburgh, to a small house at 7, Milborne Grove, South Kensington. Kipping then worked with Armstrong for a time, first on certain problems connected with colour and constitution and then on the products of the action of sulphuric acid on camphor, one of which was shown to be 3 : 4-dimethylacetophenone (*p*-acetyl-*o*-xylene).

In 1893 Arthur Lapworth arrived in Armstrong's laboratory from Birmingham, where his father was the distinguished Professor of Geology, and was placed under Kipping's supervision. Here again a very successful collaboration resulted, the work being mainly on derivatives of camphor.

Lapworth became a frequent visitor at the house in South Kensington, where he often met Pope, Forster, and other workers in Armstrong's laboratories. During one vacation when he had made no holiday plans, the Kipping's asked him to stay with them at Bridgwater : here it was that he met his future wife, Kathleen Holland.

The work of Perkin, Kipping, and Lapworth has left a lasting impression on experimental and theoretical organic chemistry which may best be realised if we attempt for a moment to consider what the record of the years 1895—1930 would be if the work of these three men, who married three sisters, were left out of consideration.

Kipping found little time for recreation, but whenever possible he and his wife went for long rowing excursions on the Thames, returning only when the light faded. During six years they heard, from the gallery of Covent Garden Opera House, nearly all the great operas and most of the famous singers of the day.

In 1897 Kipping was elected to the Royal Society at the age of 34 and soon afterwards was appointed to the Chair of Chemistry at University College, Nottingham, in succession to Professor Frank Clowes. He found the laboratories and class-rooms in Shakespeare Street compact and well-arranged but there were only four full-time students who were working for the Associateship of the Institute of Chemistry; the remainder consisted of a few ill-prepared part-time students of Engineering. Most of the evening students were working for the qualifying examination of the Pharmaceutical Society. He refers to certain short courses given in those early days to students of mining, dyeing, plumbing, and brewing, and adds " I came to the conclusion that such so-called technical education was valueless. . . . the more intelligent students of these subjects were encouraged to attend the evening classes in pure chemistry during two or three years and their practical work was so arranged that it had a direct bearing on their daily occupations." The number of students of chemistry steadily increased and Kipping, first unaided and then in collaboration with members of his staff, initiated various lines of research which will be considered later. He also acted as external Examiner to the federal Victoria University and to the Royal University of Ireland, and much appreciated the kindness and hospitality of Professor Dixon of Cork and Professor Senier of Galway, but greatly regretted the necessity of failing so large a proportion of the Irish candidates. Both before and after the first World War he was external Examiner to the University of Birmingham and wrote in 1942: " There the standard was high and the unfailing kindness of Professor and Mrs. Frankland with whom I stayed remains a most pleasant memory even now."

In the years before the war Kipping " enjoyed the thrills of learning golf and also played a good deal of tennis at the Nottingham Park Club." He usually played golf at Hollinwell (under the shadow of Byron's " hills of Annesley, bleak and barren ") with Professor Ernest Weekley, the well-known French scholar, on Wednesdays from about eleven to three or four o'clock. This habit was much appreciated by his students who then felt reasonably secure from his severe and searching interrogations. Golf and tennis, however, were not Kipping's only recreations. Mrs. Kipping and he found much pleasure in visits to theatres and concerts and in dancing. Mrs. Kipping was interested in social work and was for many years closely associated with the Nottingham Society for the Care of the Feeble-minded. Thus it came about that on one occasion the staff of the Chemistry Department at Birmingham were somewhat surprised to receive the draft questions for the B.Sc. examination from their External Examiner on the official note-paper of this Society! Satisfactory explanations, were however forthcoming!

At this time many holidays were spent walking in Switzerland and one visit was made to the Italian lakes. Professor and Mrs. Lapworth were their frequent holiday companions, especially in later years at Tenby.

During the first World War Kipping and his staff collaborated in the scheme for the preparation of synthetic drugs which were at that time unobtainable in Britain; he also lectured on musketry and map-reading to the Officers' Training Corps and superintended practice on a miniature rifle range in an old clay-pit.

Like all other Chemistry Departments of University rank, Kipping's laboratories were crowded after 1918 and it became necessary to find immediate temporary accommodation for the forty or fifty full-time students who wished to work for degrees of the University of London. The Shakespeare Street buildings of the College were situated between the City Library on the one side and the City Museum on the other, forming one large block which was and is a familiar and pleasing aspect of Nottingham. To meet the demand, one of the large rooms of the museum was cleared of its stuffed animals and converted into a laboratory for the more elementary and part-time students. This met the immediate needs but after 1922 it became obvious that the student population of the College would remain permanently at a much higher figure than before the war.

The College Council thereupon decided to build a new University College. Fortunately, this was made possible through the great generosity of Sir Jesse Boot, later Baron Trent, who not only purchased the splendid site now known as University Park but also defrayed the cost of the building and equipment and endowed the Chair of Chemistry, Kipping thus becoming the first Sir Jesse Boot Professor of Chemistry.

The College was opened by H.M. King George V in 1928. The dignity of the building, both

externally and internally, and the beauty of its setting are the envy of many older and richer academic bodies. The impact of a second World War on British University life has now created a need for still further expansion both of class rooms and of laboratories. Fortunately, the spacious surroundings of the new University of Nottingham afford ample opportunity for this. Kipping had the satisfaction of entering into occupation of the new Chemistry building in 1928, but for many years most of the old Department in Shakespeare Street was used for evening classes and for some day-time work. Since 1945 the building has been taken over by the City as the Nottingham Technical College, but former students will find little difference in the appearance of the laboratories, and Kipping's old research room where he did all his crystallisations and his own combustions is still the research laboratory of the Staff.

In 1936, after the College Council had, on several occasions, refused to accept his offers to resign, he retired from the Chair and was appointed Emeritus Professor of Chemistry. The Council made arrangements for him to work in his old laboratory at Shakespeare Street and there he continued research on silicon compounds for three years longer. Shortly after his retirement, the University of Leeds conferred upon him the degree of D.Sc. *Honoris causa*, in recognition of his long services to University teaching and research.

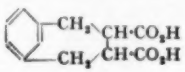
In the same year, soon after Kipping published Part L of " Organic Derivatives of Silicon," his staff and former students entertained him to dinner. Robison, the discoverer of the mechanism of the calcification of cartilage, was in the chair and over seventy were present. It was a most happy and inspiring occasion; the respect and affection in which Kipping was held were manifest in every word which was spoken. The dry humorous remarks, the caustic comments, the rather gruff encouragements stored for many years in the memories of his pupils were then released in the speeches. Happy is the man who can inspire such regard.

In 1941 he published Part LI which was unique in one respect. At the end it contained these words. " *Envoi.* As this is my last paper may I express here my sincere thanks to the Chemical Society for having published so much of my work over so long a period—F. S. K." I do not recall a similar acknowledgment by any other Fellow of the Society. Kipping's retirement was also marked by the invitation to deliver the Bakerian Lecture of the Royal Society. The subject was " Organic Derivatives of Silicon " and the lecture took place in London on a very hot summer day in 1936. Kipping afterwards expressed his deep sympathy with those who had assembled to hear it. It was, however, characteristically brief and concise even when printed, and his friends could have wished it had been longer.

On the outbreak of war in 1939 Kipping, with his wife and younger daughter, took a house on the sea-front at Criccieth and there it was my privilege to see him in 1946 and 1947. He was surrounded by the proofs of the revised, almost rewritten, edition of " Perkin and Kipping " in the production of which he had been joined by his younger son, Frederic Barry, University Lecturer in Chemistry in the University of Cambridge. He was, it need hardly be mentioned, as interested as ever in the progress of chemical research.

In the spring of 1949 the health of Mrs. Kipping caused him much anxiety, and after only a week's illness he died on May 1st in his eighty-sixth year. It was a sad, but not wholly unfitting, coincidence that the unexpected news of his death reached me in the new buildings of the University of Nottingham on the May morning of the inauguration of its first Chancellor. Some months earlier he had learned with deep satisfaction of the granting of a University Charter to the College which he had served so faithfully. His labours and those of his colleagues, Barton, Heaton, and Swinnerton, to mention only a few, had, however, secured to the College University standing and repute 40 years previously. His death removed one of the last links with what may be termed the later classical era of organic chemistry in Britain.

Kipping's first publication (*J.*, 1888, **53**, 21) was entitled " Synthetical Formation of Closed Carbon-Chains in the Aromatic Series. Part II " and described the work which was carried



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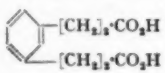

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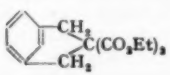


(III.)

out in von Baeyer's laboratory at Munich at the suggestion and originally under the direction of W. H. Perkin, jun. It follows a paper by Perkin in which he summarises his earlier work in the Munich laboratory and describes the synthesis of the tetrahydronaphthalene and hydrindene (indane) rings. In this paper Kipping records experiments on the action of *m*- and *p*-xylylene bromides, $C_6H_4(CH_2Br)_2$, on ethyl sodiochloromalonate in the hope of obtaining

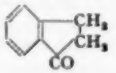
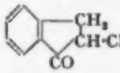
7- and 8-membered rings, on the analogy of Perkin's work with *o*-xylylene bromide. The desired compound (I) was, however, not obtained, but rather (II); the *p*-xylylene bromide derivative behaved in a similar manner with iodine.

It will be remembered, in passing, that von Baeyer's Strain Theory was partly built upon the experimental results of W. H. Perkin in which Kipping was so greatly interested.

Kipping also attempted to obtain the tetrahydro-*meta*-naphthalene derivative (III) from *m*-xylylene bromide, ethyl malonate, and two molecular proportions of sodium ethoxide, but only a resin was produced. Furthermore, he showed that no anhydride was obtainable from (II) or from the corresponding *p*-derivative.

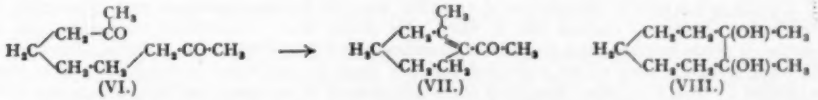
These results are what we should now expect from such reactions, but 62 years ago it was necessary to establish the facts by experiment. Here it may be mentioned that on one occasion the vapours of xylylene bromide entered von Baeyer's " Dienstwohnung " which adjoined the laboratory. He gave Kipping a " dressing down."

It is of interest to recall that, eleven years later in 1901 in collaboration with Hunter, Kipping described two 7-membered ring compounds, which he named pheno-α-ketoheptamethylene and pheno-α-aminoheptamethylene, by ring closure of the acid chloride of phenyl-*n*-valeric acid and reduction of the oxime of the ketone. The presence of the ring of seven carbon atoms was shown by the formation of phthalic acid on oxidation of the ketone by dilute nitric acid. This " internal " Friedel–Crafts reaction was also used by Kipping in the preparation of keto-tetrahydronaphthalene and of hydrindone (IV) (now indanone) and its 2-methyl derivative (V) and, as will be seen later, played an essential part in the development of much of his work.

(IV.)   (V.)

In the next two or three years Kipping, in collaboration with Perkin, devoted much attention to the preparation of ketones such as 1 : 4-diacetylbutane, 1 : 5-diacetylpentane, and 1 : 5-dibenzoylpentane by means of the ethyl acetoacetate synthesis. On the analogy of the formation of mesityl oxide and of pinacol from acetone, it appeared possible that dehydration and reduction of such diketones might be confined to one molecule giving rise to an unsaturated cyclic ketone and a cyclic pinacol respectively.

By dissolving 1 : 5-diacetylpentane (VI) in sulphuric acid, the expected product (VII) was obtained. The suggestion by Kipping and Perkin (see above) that reduction of 1 : 5-diacetylpentane might give rise to an " internal " pinacol was upheld shortly afterwards when they showed that with sodium and moist ether dimethyldihydroxyheptamethylene (VIII) was produced.



(VI.) (VII.) (VIII.)

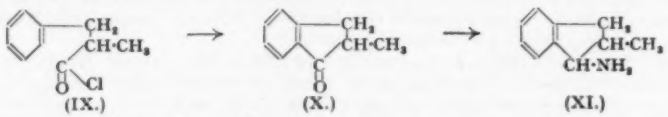
We must now refer briefly to some work of Kipping's which, apart from his Munich Ph.D. Thesis (*J.*, 1888, **53**, 21), was the first which he published independently. Between 1870 and 1893 in three papers he described the preparation of the higher dialkyl ketones by the distillation of the corresponding fatty acids with phosphoric oxide. Using this method, he prepared dihexyl and dioctyl ketones and several homologues. The research was only of preparative importance, but it was significant because so much of his later work in different fields may be regarded as a direct consequence. Thus, in an unsuccessful attempt to prepare dibenzylacetone, $(C_6H_5{\cdot}CH_2{\cdot}CH_2)_2CO$ he heated β-phenylpropionic acid with phosphoric oxide. The products were found to be the hydrocarbon " truxene," $(C_9H_4)_x$, and a small quantity of the cyclic ketone hydrindone (IV). The importance of this work lies, however, not in its relation to truxene but because Kipping was led to prepare a considerable quantity of α-hydrindone (*J.*, 1894, **65**, 480) by the self-condensation of β-phenylpropionyl chloride in ligroin solution in presence of aluminium chloride.

Three years later Revis and Kipping (*J.*, 1897, **71**, 239) continued the study of hydrindone and its condensation products and reduced its oxime with sodium amalgam in dilute acetic acid to hydrindamine, an experiment which was fated to influence much of his future work (see pp. 854, 855). Later, Kipping and Hall (*J.*, 1900, **77**, 467) obtained indene by distillation of

hydrindamine hydrochloride and of trimethylhydrindonium iodide and showed that the product was identical with that obtained by other methods.

A paper (*J.*, 1901, **79**, 602), which cannot be summarised here, is important because it contains a discussion of the significance of the terms " partially racemic " and " racemic."

It is instructive to notice how Kipping's interest in cyclic systems kept pace with his growing attraction to stereochemical problems. An instance of this, and perhaps the most important on account of its influence on his future work on optically active compounds of silicon, is to be found in his synthesis of (±)-methylhydrindamine (XI) carried out with Clarke (*J.*, 1903, **83**, 913) by reduction of the oxime of methylhydrindone (X) obtained by cyclisation of α-benzylpropionyl chloride (IX).



(IX.) (X.) (XI.)

The base contains two asymmetric carbon atoms and therefore exists in two (±)-forms which were studied by Tattersall and Kipping (*J.*, 1903, **83**, 918). Crystallisation of their salts with optically inactive acids and of their benzoyl derivatives and platinichlorides failed to effect a complete separation, although the existence of the two (±)-forms, which were designated *dl*-methylhydrindamine and *dl-neo*-methylhydrindamine, was easily demonstrated. Separation was finally effected by crystallisation of the (+)-bromocamphorsulphonates from water, without resolution of either base. The resolution of the two partially racemic [(±)-B, (+)-A] salts so obtained was then attempted. On crystallisation from boiling ethyl acetate the (±)-*neo*-methylhydrindamine salt was not resolved, but (±)-methylhydrindamine (+)-bromocamphorsulphonate finally yielded its two components, and pure (+)- and pure (−)-methylhydrindamine hydrochlorides were obtained. The (+)-bromocamphorsulphonates of the (+)- and the (−)-methylhydrindamines as separated by ethyl acetate were each shown to be mixtures of two isomeric salts; this was later found to be due to the existence of two stereoisomeric *cis*- and *trans*-modifications of bromocamphorsulphonic acid. References to this phenomenon, which was exhaustively studied by Kipping in connection with (±)-hydrindamine and (±)-menthylamine are given in *J.*, 1905, **87**, 636. Kipping's resolution of (±)-hydrindamine is described in *J.*, 1903, **83**, 873, 889.

So far we have considered the development of one main trend of Kipping's work—the investigation of cyclic compounds leading, as we have seen, to a serious interest in stereochemical problems, in the study of which the halogeno-camphorsulphonic acids played a large part.

Kipping's interest in derivatives of camphor was due to his association with Armstrong at the Central Technical College (see p. 850). He states that " Armstrong then asked me to examine a crude sulphonation product of bromocamphor prepared by W. J. Pope; thus began the joint research work which extended over six years during which many joint papers were published." The first paper described the sulphonation of camphor and bromo-camphor with anhydrosulphuric acid or chlorosulphonic acid. " The optically inactive, or feebly active, mixture of sulphonic chlorides prepared from the acid obtained by either of these methods shows a very remarkable behaviour; it is deposited from solution in well-defined crystals which, although apparently homogeneous, are simply mixtures of the two active compounds in variable proportions and are partially resolved into enantiomorphous forms on recrystallisation."

" The sulphonic derivatives of bromo- and chloro-camphor are remarkable for the extraordinary facility with which they crystallise; the sulphonic chlorides, the amides, the acids and a number of salts are described, the optical and crystallographical characters of many of the compounds being given." Such details appeared in many subsequent papers published by Kipping, both in collaboration with Pope and with other workers. The importance attached to crystallography by other pupils of Armstrong, *e.g.*, Lowry, is well known.

The authors add " Speaking generally, the sulphonic derivatives of camphor are compounds of exceptional beauty " (here, surely, we detect the Perkin touch) " and judging from the results thus far obtained will probably lead to conclusions of considerable importance." When we consider the part played by bromocamphorsulphonic acid in almost every study of optically active bases during the last 50 years, this prophecy may be regarded as entirely justified.

In two further communications Kipping and Pope showed that the preliminary effervescence observed during the combustion of sulphonic halides of camphor and its halogen derivatives

is due to evolution of sulphur dioxide and formation of the so-called π-halogen derivatives (so named owing to their pyrogenic formation), in which the atom thus introduced replaces the —SO_2Hal group in the CH_2·C(Cl)—CH_2·SO_2Hal residue of camphor. Thus bromocamphorsulphonic chloride yields α-bromo-π-chlorocamphor.

Many derivatives of this type were obtained and, in several papers published in collaboration with Lapworth, their properties and those of other derivatives of camphor, especially nitrocamphor and camphoric acid, were carefully examined. Lowry's work on bromocamphor, mutarotation, and similar themes was also an outcome of the assiduous cultivation of the camphor field in South Kensington at the turn of the century.

Reference may here be made to two stereochemical investigations in one of which Kipping and Salway approached the vexed question of the "Arrangement in Space of the Groups combined with the Tervalent Nitrogen Atom" and the other, where, with his student, Peters, he investigated "Iodonium Compounds of the Type IR′R″R‴ and the Configuration of the Iodine Atom" (*J.*, 1902, **81**, 1350). The work on the tervalent nitrogen atom may conveniently be summarised by quoting from the *Annual Reports* of the Chemical Society (1904, **1**, 144): "Kipping and Salway refer to the discrepancies between the theory of Hantzsch and Werner . . . and the failure of previous attempts to resolve bases in which three different groups are attached to tervalent nitrogen; they point out that the latter experiments are indecisive owing to the possibility of a change in the valency directions attending the conversion of ter- into quinque-valent nitrogen and *vice versa*. They treated *d*-hydrindamine, *l*-methylhydrindamine, *l*-menthylamine and *l*-phenylethylamine with *d*-benzylmethylacetyl chloride and in each case obtained but one acetyl derivative of the primary or secondary base; if the three nitrogen valency directions do not lie in one plane the production of stereoisomerides would be anticipated. . . . It is pointed out that on treating an optically inactive base with an externally compensated acid chloride, only one acidic derivative (*i.e.*, the substituted acid amide) should be formed if the original base is potentially inactive, whilst two isomerides are capable of formation if the base is externally compensated.

"Thus *dl*-hydrindamine yields two isomeric acidic derivatives with *dl*-benzylmethylacetyl chloride, whilst methylaniline, *p*-toluidine, benzylaniline and phenylhydrazine yield but one product in each case. . . . It is therefore concluded that the three valency directions of tervalent nitrogen lie in the same plane."

In the same paper it was shown that (±)-hydrindamine and (±)-α-phenylethylamine may be resolved by the aid of (+)-benzylmethylacetyl chloride, but in neither case was it possible to regenerate the optically active bases by hydrolysis of the substituted amides.

These discussions of 45 years ago are interesting in view of Prelog and Wieland's recent claim (*Helv. Chim. Acta*, 1944, **27**, 1127; *Brit. Abs.*, 1945, *A*, *II*, 100) that Tröger's base (obtained from *p*-toluidine and formaldehyde and synthesised by an unambiguous method; Spielman, *J. Amer. Chem. Soc.*, 1935, **57**, 58) can be resolved by chromatographic adsorption on activated lactose hydrate.

The work on iodonium compounds consisted in the fractional crystallisation of phenyl-*p*-tolyliodonium (+)-bromocamphorsulphonate. No evidence of resolution could be obtained.

Kipping's work on organic derivatives of silicon was commenced with the object of obtaining compounds of which the optical activity was due to the presence of an asymmetric silicon atom and clearly arose out of his work on the stereochemistry of nitrogen. This, in its turn, was a consequence of his still earlier interest in camphor. It might be imagined that the discovery of the Grignard reagent was a determining factor in Kipping's choice of this field of research; but although the progress of his work was greatly eased by the use of these reagents (*J.*, 1907, **91**, 209), the research was commenced one or two years before 1900 (the year in which Grignard made his initial observation) and in Part I Kipping and Lloyd (*J.*, 1901, **79**, 449) make no reference to the French chemist's discovery.

Kipping's work in this field falls under three main headings: (1) experiments connected with the preparation and resolution of asymmetric compounds of silicon, (2) work on the structure of the simpler condensation products derived from compounds of the type $R_2Si(OH)_2$ and $RSi(OH)_3$, and (3) the study of the products obtained from arylchlorosilanes, R_2SiCl_2 or R_3SiCl, and sodium. Of these three main lines, only the first attracted great attention at the time. Since 1940 the second line of work has been greatly extended by the Dow Corning Corporation, who have placed numerous polymers of the composition $(R_2SiO)_x$, etc., on the market.

Kipping certainly spoke truly when, in 1912, he remarked to a student who had used the term "polymerisation" loosely and rather carelessly: "polymerisation, that's a blessed word,

it's like Mesopotamia." The personal application of this comment was not apparent for nearly 30 years. His former students and colleagues welcome the utilisation of his silicols and silicones but deny with much warmth that this publicity adds anything to his scientific reputation, which was firmly established many years before the plastic age commenced.

The reactions employed by Kipping for the synthesis and, in three cases, resolution of his asymmetric compounds were simple in the extreme but the experimental difficulties were considerable. In Part I three chlorine atoms of silicon tetrachloride were successively replaced by the phenoxy-, methoxy-, and ethoxy-groups, but attempts at resolution by replacing the fourth chlorine atom by the menthoxy-group or by the anion of an optically active acid were unsuccessful. Five other asymmetric compounds of silicon were prepared between 1905 and 1910 by the successive replacement of the chlorine atoms with alkyl and aryl radicals by means of the Grignard reagent.

The sulphonic acids of (±)-benzylmethylethylpropylsilane and (±)-benzylmethylpropyl-*iso*butylsilane (then " silicanes ") resisted all attempts at their resolution, although numerous optically active bases including cinchonidine, cinchonine, (−)-menthylamine, strychnine, brucine, and quinine were employed. Kipping's first success was obtained by sulphonation of (±)-phenylbenzylethylpropylsilane. When sulphuric acid is used at ordinary temperatures or below 70°, benzene is eliminated (but not toluene), probably with formation of $SiEtPr(CH_2Ph)\cdot OH$ which then yields the disulphonic acid of the oxide, *i.e.*, $O[SiPrEt(CH_2\cdot C_6H_4\cdot SO_3H)]_2$. This elimination of benzene appears to be characteristic of the Ph–Si link under such conditions. Later, he used chlorosulphonic acid instead of sulphuric acid, obtaining the same sulphonic acid.

Kipping finally isolated a crystalline, deliquescent diammonium salt of this acid, of which he remarks in a footnote " This was the first crystalline silicon compound obtained during at least six months' work so the author has been careful not to over-rate its beauty." This acid was also prepared by the sulphonation of benzylethylpropylsilicol, obtained by the action of water on the corresponding chloride (Part II) and also (*J.*, 1908, **93**, 198) by sulphonation of benzylethylpropylsilyl oxide, $O(SiR_1R_2R_3)_2$. Kipping then conclusively showed by numerous analyses of the (−)-menthylamine salt, that the sulphonic acid was a derivative of the oxide and not of the silicol. Attempts to resolve this acid by fractional crystallisation of the (−)-menthylamine, (+)-bornylamine, cinchonidine, cinchonidine hydrogen, and strychnine salts were unsuccessful, but with (+)-methylhydrindamine resolution was accomplished, though much care was needed in interpreting the results owing to the low specific rotation of the (+)- and the (−)-sulphonic acid. Thus on crystallising the (−)-methylhydrindamine salt of the (±)-acid, sparingly and readily soluble fractions, differing widely in m. p. but not in specific rotation, were obtained (Part II). Expulsion of the volatile base and conversion into the (−)-menthylamine salts gave products which did not differ appreciably in either m. p. or specific rotation. By suitable alternate use of the volatile (−)- and (+)-methylhydrindamines by methods which are obvious and need not be described in detail it was conclusively proved that resolution had occurred, the *d*A*d*B, *l*A*l*B, *d*A*l*B, and *l*A*d*B salts (where A and B represent acid and base), being very carefully compared. Finally, by removal of the volatile bases, two sodium salts of specific rotation +5·8° and −5·9° were obtained (Part VI; *J.*, 1908, **93**, 457).

It is interesting to speculate as to whether, had it not been for the unexpected elimination of the phenyl group during the sulphonation of phenylbenzylethylpropylsilane, Kipping would ever have studied the sulphonation of an asymmetric silicol or oxide. Had he not done so, the negative results obtained with two sulphonated silanes suggest that success might never have been achieved. Still more remarkable is the coincidence that the only bases which were found capable of resolving the sulphonated silicyl oxides were (+)- and (−)-methylhydrindamine which he had himself prepared for the first time in the course of earlier work and submitted to a most exhaustive examination (see p. 854).

A year or two later, in collaboration with B. D. W. Luff, Kipping carried out a successful resolution of the disulphonic acid of (±)-benzylethyl*iso*butylsilyl oxide, also by the aid of (+)- and (−)-methylhydrindamine, thus amplifying and confirming his earlier results. In this case the specific rotations of the sodium salts were larger, +10·4° and −10·5°.

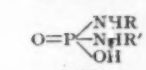
Several years later Kipping prepared (±)-dibenzyldiethyldipropylsilicoethane and obtained brucine and (−)-menthylamine salts of the disulphonic acid. Separation of the racemic and *meso*-forms of the acid or the resolution of the first-named was not effected, owing to lack of material (Part XXIV; *J.*, 1921, **119**, 647). With reference to this hydrocarbon and the corresponding diphenyl compound, Kipping writes " although their molecules contain linked

silicon atoms both silicohydrocarbons are attacked only very slowly if at all by boiling aqueous alkalis and even when they are warmed with sodium methoxide in methyl alcohol or acetone no rapid evolution of hydrogen is observed. The grouping >Si–Si< is not necessarily unstable to alkalis, and whether the silicon atoms become separated or not is determined by the nature of the atoms or groups with which they are combined." The behaviour of the >Si–Si< link towards alkali is mentioned on p. 858.

During the purification of benzylethylsilicon dichloride which was so important an intermediate compound in much of his work, Kipping isolated dibenzylethylsilyl chloride, $SiClEt(CH_2Ph)_2$. This was converted into dibenzylethylpropylsilane and sulphonated by means of chlorosulphonic acid in chloroform (Part XII; *J.*, 1910, **97**, 142). After separation of the mono- and di-sulphonic acids by means of their strychnine or (−)-menthylamine salts, the monosulphonic acid was successfully resolved by brucine but by no other base, although several were employed (see p. 859). Nothing could be more striking than the behaviour of the brucine salt on recrystallisation as compared with that of the other alkaloidal salts. The two end fractions of the brucine salt were then converted through the (−)-menthylamine salt into the sodium salt, of which only the (−)-isomer was obtained optically pure. Its specific rotation was certainly not greater than −1°. Concentrated solutions of the optically impure (+)-acid were, however, distinctly dextrorotatory, readings of about +0·1° being obtained (see p. 860). " These low values for the rotation and the fact that, although four pairs of salts (of the two acids) were carefully examined, in no case was there a difference in melting point or in specific rotation well outside the limit of the possible experimental error, might well have cast some doubt on the relationship of the two acids had it not been for the overwhelming evidence " (Part XIII; *J.*, 1910, **97**, 755). This evidence cannot be given in detail here, but was based on the maintenance of the properties of the two brucine salts on passage through other salts, followed by regeneration, on a considerable difference in solubility of the (−)-menthylamine salt of the (±)- and the (−)-acid, and a slight but distinct difference in m. p. Furthermore, numerous tests established the chemical identity of the resolution products and the absence of impurity. When Kipping described this work at a meeting of the Chemical Society in March 1910, he concluded by saying: " If you will do us the honour of reading our paper I think you will be convinced that we have established our conclusions."

Shortly afterwards, Kipping and T. A. Smith (*J.*, 1913, **103**, 2034) prepared the tin analogue of the silane, dibenzylethylpropylstannane, $SnEtPr(CH_2Ph)_2$, but the sulphonation of this and of dibenzyldiethylstannane was impossible owing to the elimination of both the benzyl groups by the acid.

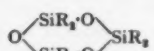
About this time Kipping returned to the study of a similar problem on which Caven (*J.*, 1902, **81**, 1362) had already carried out experiments in his laboratories—the stereochemistry of asymmetrical derivatives of phosphoric acid. Caven had been unable to resolve compounds of the type (XII). Kipping and Luff prepared phenyl *p*-tolyl hydrogen phosphate $OP(OPh)(OC_7H_7)\cdot OH$ and crystallised its salts with eight optically active bases without effecting resolution. Evidence that the acid was, in fact, a (±)-compound was obtained by the separation of the (±)-hydrindamide into two inactive compounds, the [*d*A*d*B, *l*A*l*B] and the [*d*A*l*B, *l*A*d*B] isomers (see p. 855). By crystallisation of the (+)-hydrindamide and (−)-menthylamide, two fractions differing in m. p. and specific rotation were obtained in each case, indicating a resolution of the (±)-acid. Similar results were obtained by Kipping and Challenger with the (−)-menthylamide of phenyl β-naphthyl hydrogen phosphate. In none of the cases was it possible to remove the optically active ·NHR group by hydrolysis so as to obtain the corresponding acids. This stability appears to be characteristic of amides and substituted amides of this type. Over 30 years later, Davies and Mann (*J.*, 1944, 276) pointed out that these and similar experiments aiming at the isolation of the optically active acids were foredoomed to failure owing to resonance.


(XII.)

Kipping's investigations on the condensation and dehydration products of the dibenzyl- and diphenyl-silanediols, $R_2Si(OH)_2$, were laborious and involved much detailed study of closely related substances and the manipulation of intractable oils, many of which were finally induced to crystallise. He realised from the beginning (see Part X; *J.*, 1909, **95**, 302) that the various so-called silicones, *e.g.*, $SiOEt_2$, $SiOPh_2$, and SiOPhEt, were associated and not simple molecules; this was, in fact, stated by Dilthey in the case of the diphenyl derivative in 1905. In his first paper with Robison (*J.*, 1908, **93**, 439) Kipping studied the loss of water from dibenzylsilanediol $Si(CH_2Ph)(OH)_2$, and in Parts XVIII and XX established that under various conditions the diol can yield trianhydrotrisdibenzylsilanediol (XIII), dianhydro-

trisdibenzylsilanediol $HO{\cdot}SiR_2{\cdot}O{\cdot}SiR_2{\cdot}O{\cdot}SiR_2{\cdot}OH$, and anhydrobisdibenzylsilanediol $HO{\cdot}SiR_2{\cdot}O{\cdot}SiR_2{\cdot}OH$, where $R = CH_2{\cdot}C_6H_5$. Heat or alcoholic hydrogen chloride, acetyl chloride, or alkali were employed as condensing agents.

During this period a similar and even more extensive study of the condensation products of diphenylsilanediol was carried out, and in three papers (Parts XVI, XVII, and XXI, *J.*, 1912,



(XIII.)

$HO{\cdot}SiPh_2{\cdot}O{-}SiPh_2{\cdot}OH$

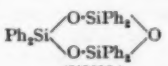
(XIV.)

$HO{\cdot}SiPh_2{\cdot}O{\cdot}SiPh_2{\cdot}O{\cdot}SiPh_2{\cdot}OH$

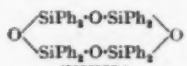
(XV.)

$HO{\cdot}SiPh_2{\cdot}O{\cdot}SiPh_2{\cdot}O{-}SiPh_2{\cdot}O{\cdot}SiPh_2{\cdot}OH$

(XVI.)



(XVII.)



(XVIII.)

101, 2108, 2125; 1914, **105**, 484) the existence of five crystalline condensation products was established, namely, (XIV)—(XVIII). Crystallographic measurements were carried out on four of these products.

When dichlorosilanes of the type $RR'SiCl_2$ are decomposed with cold aqueous ammonia, the corresponding diols, *e.g.*, benzylethylsilanediol and phenylethylsilanediol, $RR'Si(OH)_2$, are obtained (Part XIX; *J.*, 1912, **101**, 2156), and from the second of these the crystalline condensation product $HO{\cdot}SiPhEt{\cdot}O{\cdot}SiPhEt{\cdot}OH$ can be isolated. Kipping refers to the ease with which these two diols yield oily condensation products, and adds: "as the components of these mixtures have doubtless much lower melting points than the corresponding derivatives of diphenylsilanediol they cannot be isolated by the methods which were found to be of service in the case of the latter compounds." These substances containing alkyl groups foreshadowed the numerous polymers derived from $Alkyl_2Si(OH)_2$ which have since found such important technical applications.

With his student Meads (*J.*, 1914, **105**, 679; 1915, **107**, 459) he also examined the condensation products obtained by the hydrolysis of phenyltrichlorosilanes which are derived from four, five, six, or more molecules of $PhSi(OH)_3$. Here and elsewhere he drew attention to the possible analogy between the structure of these compounds and that of the silicates, and between $HO{\cdot}Sn(C_7H_7)_2{\cdot}O{\cdot}Sn{\cdot}(C_7H_7)_2{\cdot}O{\cdot}Sn(C_7H_7)_2{\cdot}OH$ and the polymeric stannic acids. He also found that $(C_7H_7)_3Sn{\cdot}OH$ is strongly associated in benzene solution (*J.*, 1913, **103**, 2034).

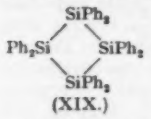
It is a pleasure to recall that the Dow Corning Corporation presented him in 1945 with a complete set of his 50 papers on Organic Derivatives of Silicon very clearly typed on strong paper and bound in boards made from a "silicone" polymer. These three volumes he presented to the Royal Society and they have been of great help in preparing this memoir.

No one who worked in the Nottingham laboratories between 1907 and 1910 will have forgotten the riddle of the constitution of the yellowish-white, amorphous, insoluble organic substances which are produced as by-products when any Grignard compound reacts with silicon tetrachloride. When all organo-silicon halides are removed from the magnesium salts with ether, and the salts dissolved in water, these compounds remain. Their most striking property is the rapid effervescence of hydrogen which takes place on addition of potassium hydroxide (see Part X). Kipping never published a full account of these substances though he worked on them from time to time. It soon became clear that they contained $\gtrless Si{-}Si \lessgtr$ links. The evolution of hydrogen seems analogous to that observed when silicoethane Si_2H_6, silico-oxalic acid $H_2Si_2O_4$, silicomesoxalic acid and similar compounds are treated with alkali. For the ethyl compound, Martin and Kipping (*J.*, 1909, **95**, 302) suggested the possible structure $C_2H_5Si(OH)_2{\cdot}SiO_2H$. The formation of such compounds was particularly marked in the case of the *cyclo*hexyl derivatives, volatile chlorides containing $\gtrless Si{-}Si \lessgtr$ links being detected (Part XLII, *J.*, 1930, 1020) and light thrown on their method of formation.

Later it was found that wet piperidine was a more satisfactory reagent for the fission of the $\gtrless Si{-}Si \lessgtr$ link and the hydrogen evolved—the "hydrogen number"—was frequently employed as evidence of structure (see Part XXVI, *J.*, 1921, **119**, 848) although the reaction was not of universal application, a few compounds such as $Si_2(C_6H_5)_2$ and $Si_2(C_6H_5)_2(C_2H_5)_2(C_3H_7)_2$ being found to resist fission (see above).

Kipping also gave much attention to the reaction between sodium and organo-silicon halides of the type R_2SiCl_2 and R_3SiCl. The original object was to obtain a simple unsaturated

compound $R_2Si{:}SiR_2$ but this was never achieved. Diphenylsilicon dichloride, for instance, gave two crystalline compounds of the formula Si_4Ph_8, one of which in later work was shown to be octaphenyl*cyclo*silicotetrane (XIX), whereas the constitution of the other " is best represented by $\cdots SiPh_2{\cdot}SiPh_2{\cdot}SiPh_2{\cdot}SiPh_2\cdots$. This is much more reactive than the cyclic compound. It slowly changes on exposure to light and air and undergoes atmospheric oxidation in toluene at 100° and combines with iodine at ordinary temperature (*J.*, 1923, **123**, 2590).



(XIX.)

In 1932, Kipping and Blackburn (Part XLVI, *J.*, 2200) showed that nitration of tetraphenylsilane yielded a small amount of a pure nitro-compound which, on decomposition with bromine, gave *m*-bromonitrobenzene. The main product of nitration, however, was extremely ill-defined and with bromine yielded a mixture of *m*- and *p*-bromonitrobenzene approximately in the proportion of 2 : 1. The occurrence of *o*-nitration was not established. The pure tetranitro-compound was reduced to the corresponding amine, which was thoroughly examined.

Part L of " Organic Derivatives of Silicon " (*J.*, 1935, 1088) is noteworthy as marking the author's Jubilee and also because it emphasised his definite, though late, entry into the field of aromatic substitution. Had he undertaken work of this kind earlier most interesting results would no doubt have been forthcoming. The paper describes the nitration of phenyltriethyl-, diphenyldiethyl-, and triphenylethyl-silanes, $PhSiEt_3$, Ph_2SiEt_2, and Ph_3SiEt. Examination of the bromonitrobenzenes obtained from the crude products of nitration showed that *m*-nitration diminishes and *p*-nitration increases as the phenyl groups are replaced by ethyl groups : " $-SiPh_3$ in fact is more strongly *m*-orientating than $-CCl_3$, although rather less so than NO_2."

When more than two phenyl groups were present in the silanes the nitration product was of a very ill-defined nature. Kipping thought it probable that *m*- and *p*-nitration might occur in the same molecule.

My association with Kipping began in December 1907, when I went to see him about a small research scholarship which was advertised at Nottingham. I well recall the rather searching questions he asked about the underlying object of some exploratory experiments in research on which I had been engaged for a few weeks at the suggestion of a former teacher. The research scholarship was awarded to someone else, but Kipping made arrangements which enabled me to begin work with him in the following January. At that time new research students were told to prepare (±)-methylhydrindamine (*J.*, 1903, **83**, 913) starting from ethyl benzylmethylacetoacetate. During this preliminary initiation or very shortly afterwards I first heard addressed to me, the words so familiar to all of Kipping's students—" you started out with 50 grams of ester, you now show me 5 grams of this stuff. *Where's it all gone to?* " There was often no answer !

During 1907 Kipping had published (*J.*, **91**, 209) his account of the resolution of the disulphonic acid of benzylethylpropylsilyl oxide by means of the (+)- and (−)-methylhydrindamines. Having succeeded in establishing the capacity of asymmetric compounds of silicon to give rise to optical activity, he wished to confirm this by finding other examples. I was therefore given a crude fraction containing dibenzylethylsilyl chloride $(Ph{\cdot}CH_2)_2SiEtCl$ and told to purify it, replace the chlorine atom by a propyl group by means of the Grignard reaction, sulphonate *one* benzyl group, and resolve the resulting dibenzylethylpropylsilanemonosulphonic acid.

The somewhat painful " breaking in "—or perhaps " breaking down "—process undergone by all who wished to serve Kipping, the oft-repeated preparation of more material, the separation of the monosulphonic acid from the disulphonic acid (simultaneously produced) by fractional crystallisation of the strychnine or (−)-menthylamine salts (which did not resolve the acid), and the final preparation of the sodium salt by removal of the base occupied over a year. Months were then spent in trying one optically active base after another in the hope of effecting resolution but, as in the case of two other benzylsulphonic acids containing only one atom of silicon (*J.*, 1907, **91**, 717; 1909, **95**, 69), without success. Kipping decided one morning to give up the struggle and publish the preparation of the acids and the negative experiments on resolution and to " get on with " something else, but—" have you tried brucine? " He was told that it was the only available alkaloid which we had not tried. Then—" how much sodium salt have you still got? " The answer—" about one gram "—decided him. " We may as well try brucine " he said. Then—to quote the joint paper which Kipping wrote later—" the

brucine salt could hardly be recrystallised without its affording clear evidence of physical heterogeneity."

But there was no more material on which further experiments could be made and—this was in May—it was not till the end of November 1909 that enough of the two brucine salts could be collected to warrant a conversion through the (−)-menthylamine salts into the two sodium salts. The brucine salts differed in m. p. by about 100°, but the (−)-menthylamine salts by only about 1·5°. At last the sodium salt from the sparingly soluble fraction of brucine salt was examined polarimetrically. The specific rotation was about −1°. Kipping was informed. " You know what I think," he said. He was assured that the rotation was *not* due to traces of brucine or (−)-menthylamine. With trepidation the sodium salt from the other end was prepared and dissolved. I went home for tea. On returning in the evening, I placed the tube in the polarimeter and a slight dextrorotation was observed. (The preparation had never been near a dextro-rotatory base.) A fellow research worker was asked to say what he thought of the two yellow half-circles. " Dextro "—was the answer. Kipping was informed by telephone—with careful suppression of any natural exuberance. " *Well* "—pause—" we shall be able to get on now." Nothing more ! Two years hard labour—two years in which I, in common with others, had only been sustained by the words quoted by Seton Merriman in one of his novels then so much the vogue—" he who has lost all hope has also lost all fear." Two such years—during which at times the sight of the *Journal of the Chemical Society* was almost a pain, so remote did success and possible publication appear—might have warranted slightly warmer congratulations. But the Master had trained us well. We did not expect much. . . .

The morning however was yet to come. . . . Kipping looked through the tube. The sodium salt had been dried at 100° and the solution on standing overnight had formed a very slight suspension. " The sooner you learn that you can't take a rotation in a turbid solution the better," he remarked. The specific rotation was about +1·5°, lower even than the figures obtained for the first optically active silicon compound in 1907. This did not trouble Kipping, however, as a further study of the behaviour of the (+)- and (−)-sodium salts afforded decisive evidence of resolution. It was also shown that the sulphonic acid group was not situated in the CH_2 of the benzyl group.

A few days after the resolution Kipping came down with several small filter flasks and Büchner funnels for use in the examination of the properties of salts of the optically active acids. The future work was outlined. " How soon do you think you'll finish examining these salts ? " " In about 3 weeks " was rather tentatively suggested, producing the comment in the characteristic deep voice which we feared and imitated—and loved—" I don't suppose you will." He was right.

When the work was collected in the form of two joint papers, I, like others of his students in similar circumstances, was told that I was to " read " the first one dealing with the preparation and purification of the sulphonic acids before the Chemical Society in London. Thereupon followed a somewhat embarrassing, but very valuable, rehearsal in a small class room with the Professor as sole audience. At a later meeting of the Society it was my privilege to hear him give an extraordinarily lucid account of the resolution experiments. H. B. Dixon, who was in the Chair, described the work as a combination of genius and patience. Lest one should be exalted overmuch, W. N. Haworth, who knew Dixon well, explained shortly afterwards that he doubtless meant that the genius was Kipping's and the patience his student's. No doubt he was right, but, looking back, I feel that much of the patience must also have been exercised by Kipping—in spite of occasional suggestions to the contrary. Years afterwards one of his students expressed his indebtedness to the Professor " for his kindly patience and even more for his kindly impatience." The patience and understanding predominated. To a student who proposed to apply for a scholarship for which he was not really fitted at the time he said—and his manner was quite different from his everyday habit—" you're not ripe yet, but it will come."

An expert manipulator, especially of small quantities of material, Kipping had an uncanny facility for detecting an impurity, for removing it, and for causing intractable gums to crystallise. He was sceptical of all results not thoroughly substantiated.

His students will never forget the experiments which he used to carry out at their benches, using only test-tubes and glass rods. " Why can't you get some glass rods ? They're cheap enough " he would say when one's supply failed. Greenaway (" The Life and Work of Professor William Henry Perkin," The Chemical Society, 1932, p. 15) writes : " Baeyer, as is well-known, worked on a small scale, mainly in test-tubes of which large numbers were kept in racks in his private laboratory. Wide-mouthed bottles containing a large stock of glass rods were

also there, and small flasks, beakers, etc. A striking feature was the absence of large apparatus." These lines might have been written of Kipping.

He was a man of few words, whether spoken or written. On visiting a student his greeting was usually—" Well ? " If he expected very little there was sometimes no greeting at all—he just waited. On leaving he would say—" Well, get on with it ! " or " keep busy." On one occasion he gave this valuable advice : " You want to get up in the morning and think out ten times as much as it's possible to do, and then come down and do it."

Once with his rather picturesque exaggeration he said, " If —— says a substance is pure he means there's 50 per cent. there and if he says its crude then there's none there at all." He had a horror of what he called " a mare's nest " and always invoked this zoological phenomenon as the most probable explanation of his students' results, especially if the results had long been hoped for.

An all-round athlete himself, he encouraged his students in the many-sided activities of College life. He even sympathised when these occupied too high a proportion of their time. " So-and-so is a very nice fellow, but awfully lazy." To another, now holding a responsible position in the profession of analytical chemistry, he said " The Senate believes that you are the root of all evil in this College and I've been told to reprimand you. . . . Well " (that deep voice) " here's the reprimand ! "

After two years' absence from his laboratory I returned to work there for several weeks and met Robison, one of his earliest workers in the silicon field, who, after studying in Germany with Hantzsch and spending a period in Galway on Senier's staff, had joined Kipping as an Assistant Lecturer. He had found, as he told us, life in Connaught too soft and easy. He knew where to find the antidote. Robison, during both his periods with Kipping, worked on the condensation products of diphenyl- and dibenzyl-silanediols $R_2Si(OH)_2$ and obtained, after much almost heartbreaking labour, several beautifully crystalline condensation products. During this and similar work many viscous residues were obtained, the further examination of which appeared too daunting even to the master, whose mere presence in the laboratory was popularly said to induce the process of crystallisation. Recently these " silicone polymers " have achieved world-wide recognition as plastics, insulating materials, lubricants, and in other connections.

Shortly after this Robison joined Harden at the Lister Institute. His later work is built into the fabric of biochemistry. It is a tribute to both master and pupil that without any previous knowledge of biochemistry, but with the training and discipline of Kipping as an all-sufficient foundation, Robison should so rapidly have achieved such outstanding results.

In the years after 1912 I met Kipping from time to time when he was external Examiner to the University of Birmingham,—on one of these occasions he greatly pleased the Franklands, with whom he stayed at Northfield, by cutting their extensive lawn in war-time. After Frankland's retirement I had the privilege of entertaining Kipping in my bachelor lodgings and he was much intrigued by my landlady's parrot, whose comments somewhat disturbed our consideration of border-line cases—an occupation not facilitated by the failure of the gas one late evening in that first post-war summer of 1919. These rooms were well-known to a long succession of Frankland's staff. He also examined my first two Ph.D. students at Manchester, when he showed himself a very sympathetic inquisitor. He was, however, somewhat dismayed by the Manchester practice of admitting members of Staff and prospective Ph.D. candidates to the oral examination ! When I offered to see him off by train he refused with his characteristic desire to spare people trouble, saying—" Certainly not ; I knew London Road Station before you were born."

Dr. A. H. Salway writes :

" During the years 1900—1904, when I was privileged to be a student under Kipping at University College, Nottingham, the college was largely attended by so-called ' normal ' students aspiring to become certificated teachers under the Board of Education, and independent University students were in a minority. Of students wishing to prepare themselves for a career in the chemical profession there were not more than a dozen all told. In these conditions the Professor lectured only to the former class of students, preferring to coach the advanced chemical students privately. Thus he paved the way for many a promising pupil to take his London degree with honours as an external student.

" In those days the research students were accommodated in an underground cellar, the ' Lower Lab.,' reached by descending an iron staircase, and the equipment at our disposal was not of the ultra-modern variety seen at the present day. But that did not matter ; all we

required in our attempts to prove the asymmetry of the nitrogen atom was an unlimited stock of small beakers. If one visited the Professor's private laboratory the first objects which caught the eye were rows and rows of salt-encrusted beakers lined along the benches, with father-beaker at the head of the column and his family of small and smaller children trailing into infinity behind. And so our underground cellar became a feeble imitation of the Professor's sanctum.

"This kind of work on the intensive fractionation of ever-diminishing quantities proved such excellent training in the handling of infinitesimal amounts of material that it has been said of some of his pupils that they had only to handle a test-tube and the result was 3 pages of original observations for the *Journal*.

"Professor Kipping was a man of some pawkish humour, which, at least on one occasion, called for the remark, from one of his colleagues, 'It's that man again,' thus forestalling Mr. T. Handley by some 40 years. One example I may perhaps be permitted to recall. Sometimes his lecturers did not quite display the Professor's brilliance in capturing the ears of their listeners, so that lectures attended at first by some dozen students were apt to develop into private interviews with the lecturer. On some such occasion I was hurrying along the corridor on my way to a lecture when I encountered Professor Kipping, who slyly remarked: 'Hurry up! Dr. —— is looking for his class. Are you it?'

"Perhaps the greatest tribute Kipping's pupils can pay to his memory is that he spared himself no time or trouble to foster their well-being or to find for them suitable posts in which their respective talents might find adequate expression. In the early days of this century professional posts were not like ripe plums in an orchard, waiting to be plucked at leisure; therefore all the more credit to a Master who rarely failed to plant his pupils' feet on the first rung of the ladder.

"Personally, I feel a great debt of gratitude for his devotion to my welfare, particularly after I graduated in 1902 when I was on the point of accepting a post as science master at a grammar school. He alone made it possible for me (A. H. S.) to undertake post-graduate research and put me in the way of an 1851 Exhibition Scholarship."

It will be clear from this memoir that to work with Kipping was no easy thing. He believed with Jeremiah that "it is good for a man that he bear the yoke in his youth." The Vice-Chancellor of Leeds, when presenting him for his honorary degree, referred to his "exacting and severe standard of scientific accuracy at once the despair and the inspiration of his research students." Kipping's interest in beginners was equally great, and many tributes have been paid to the help and guidance which he gave them. To those who bore the yoke, survived the ordeal, and gave of their best, his friendly interest and readiness to help throughout the years knew no bounds.

He was an athlete and a sportsman, and it was said of him that "he owed his perennial youth in no small measure to . . . an expert manipulation of cyclic compounds on the golf course, the tennis court, and the billiard table."

Kipping's single-hearted devotion to research work undertaken for its own sake was an inspiration to many. The words of the writer of Ecclesiastes seem particularly appropriate to his life and outlook: "Cast thy bread upon the waters: for thou shalt find it after many days. . . . He that observeth the wind shall not sow; and he that regardeth the clouds shall not reap. . . . In the morning sow thy seed, and in the evening withhold not thine hand; for thou knowest not which shall prosper, whether this or that, or whether they both shall be alike good."

FREDERICK CHALLENGER.

THE CHEMICAL SOCIETY

SCIENTIFIC MEETINGS DURING APRIL, 1951

LONDON.

Thursday, April 26th, 1951, *at* 7.30 *p.m.*

Centenary Lecture, **Some Recent Advances in the Chemistry of Natural Products,** by Professor R. B. Woodward (Harvard).

ABERDEEN.

Thursday, April 26th, 1951, *at* 7.30 *p.m.*

Lecture, **Studies in Infra-red Spectroscopy,** by Dr. H. W. Thompson, M.A., F.R.S.

Joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry to be held in the Chemistry Department, Marischal College, Aberdeen.

CAMBRIDGE.

Friday, April 27th, 1951, *at* 5 *p.m.*

Centenary Lecture, **Some Recent Advances in the Chemistry of Natural Products,** by Professor R. B. Woodward (Harvard).

Joint meeting with the University Chemical Society to be held in the Large Lecture Theatre, Chemical Laboratory, The University, Cambridge.

IRISH REPUBLIC.

Wednesday, April 4th, 1951, *at* 7.45 *p.m.*

Lecture, **Humour and Humanism in Chemistry**, by Professor J. Read, M.A., Sc.D., F.R.S.

Joint meeting with the Institute of Chemistry of Ireland, the Royal Institute of Chemistry and the Society of Chemical Industry to be held in the Chemical Laboratory, Trinity College, Dublin.

Friday, April 6th, 1951, *at* 7.45 *p.m.*

Lecture, **Humour and Humanism in Chemistry**, by Professor J. Read, M.A., Sc.D., F.R.S.

Joint meeting with the Institute of Chemistry of Ireland, the Royal Institute of Chemistry and the Society of Chemical Industry to be held at University College, Cork.

Monday, April 9th, 1951 *at* 7.45 *p.m.*

Lecture, **Humour and Humanism in Chemistry**, by Professor J. Read, M.A., Sc.D., F.R.S.

Joint meeting with the Institute of Chemistry of Ireland, the Royal Institute of Chemistry and the Society of Chemical Industry to be held in the Chemical Laboratory, University College, Galway.

LEEDS.

Tuesday, April 24th, 1951, at 6.30 p.m.

Lecture, **The Use of Optically Active Compounds in the Study of Organic Reactions,** by Dr. J. Kenyon, F.R.S.

Joint meeting with the University Chemical Society to be held in the Department of Chemistry, The University, Leeds. The lecture will be preceded by a display of Scientific Films at 5 p.m.

NORTHERN IRELAND.

Thursday, April 5th, 1951, at 7.30 p.m.

Lecture, **48 Years in the Profession of Chemistry,** by Mr. R. F. Innes, F.R.I.C.

Joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry to be held in the Lecture Theatre, Department of Agriculture, Belfast.

ST. ANDREWS AND DUNDEE.

Friday, April 13th, 1951, at 5.15 p.m.

Lecture, **Laboratory Animals : their Uses and Productions,** by Mr. A. L. Bacharach, M.A., F.R.I.C.

Joint meeting with St. Andrews University Chemical Society to be held in the Chemistry Department, United College, St. Andrews.

Friday, April 27th, 1951, at 5.15 p.m.

Lecture, **Whence come Meteorites ? Views Ancient and Modern,** by Professor F. A. Paneth, Ph.D., F.R.S.

Joint meeting with St. Andrews University Chemical Society to be held in the Chemistry Department, United College, St. Andrews.

PROCEEDINGS

OF THE

CHEMICAL SOCIETY

Minutes of a

SCIENTIFIC MEETING

held at Burlington House on Thursday, February 1st, 1951, at 7.30 p.m.

DR. G. M. BENNETT, C.B., M.A., Sc.D., F.R.S., Vice-President, was in the Chair.

MINUTES.

The Minutes of the Scientific Meeting held at Burlington House on January 18th, 1951, were read, and were confirmed and signed.

FORMAL ADMISSION OF FELLOWS.

The following were admitted Fellows of the Society: Lester P. Kuhn, L. Hough, D. Thompson, John A. Mills, Lloyd M. Jackman, R. A. Thompson, R. E. Stedman, G. E. Green, N. C. Brown.

SCIENTIFIC COMMUNICATIONS.

The following papers were read and discussed:

"Experiments on the Synthesis of the Pyrethrins. Part VI. Synthesis of *trans*-Pyrethrone and *trans*-Pyrethrolone." By L. Crombie, S. H. Harper, and D. Thompson.

"Synthetic Long-chain Aliphatic Compounds. Part III. A Critical Examination of Two Methods of Olefinic Acid Synthesis." By D. E. Ames and R. E. Bowman.

"The Synthesis of Sugars from Simpler Substances. Part I. The *in vitro* Synthesis of the Pentoses." By L. Hough and J. K. N. Jones.

Minutes of a

SCIENTIFIC MEETING

held at Burlington House on Thursday, February 15th, 1951, at 7.30 p.m.

The President, PROFESSOR E. K. RIDEAL, M.B.E., M.A., D.Sc., F.R.S., was in the Chair and welcomed Professor and Mrs. L. F. Fieser (Harvard) and Professor W. G. Dauben (California), who were attending the meeting.

MINUTES.

The Minutes of the Scientific Meeting held at Burlington House on Thursday, February 1st, 1951, were read, and were confirmed and signed.

VACANCIES ON COUNCIL 1951—1952.

It was reported that the following nominations had been received:

Vice-Presidents who have not filled the Office of President. (*Three Vacancies.*)

PROFESSOR G. R. CLEMO (Newcastle-on-Tyne).
PROFESSOR D. H. HEY (London).
PROFESSOR M. STACEY (Birmingham).
PROFESSOR E. E. TURNER (London).

Honorary Secretaries. (*Two Vacancies.*)

PROFESSOR E. D. HUGHES (London).
DR. L. E. SUTTON (Oxford).

Elected Ordinary Members of Council.

Constituency I. (South-East England.) (*Three Vacancies.*)

DR. ISHBEL G. M. CAMPBELL (Southampton).
MR. H. M. POWELL (Oxford).
DR. H. N. RYDON (London).
DR. J. W. SMITH (London).

Constituency II. (Central and South-West England and South Wales.) (*Two Vacancies.*)

PROFESSOR WILSON BAKER (Bristol).
DR. E. J. BOURNE (Birmingham).
PROFESSOR C. W. SHOPPEE (Swansea).

Constituency III. (North-West England, North Wales, and the Isle of Man.) (*One Vacancy.*)

DR. G. BADDELEY (Manchester).

Constituency IV. (North-East England.) (*One Vacancy.*)

DR. T. S. STEVENS (Sheffield).

Constituency V. (Scotland.) (*One Vacancy.*)

DR. J. BELL (Glasgow).

Constituency VI. (Ireland.) (*One Vacancy.*)

DR. A. J. TURNER (Lisburn).
PROFESSOR A. R. J. P. UBBELOHDE (Belfast).

APPOINTMENT OF SCRUTATORS.

Dr. M. F. Ansell and Dr. M. J. Birchenough were appointed Scrutators for the ballot for the forthcoming election of Vice-Presidents, who have not filled the office of President, and elected ordinary Members of Council.

FORMAL ADMISSION OF FELLOWS.

The following were admitted Fellows of the Society: Louis F. Fieser, William G. Dauben, Norman H. Cromwell, D. W. Neill, H. G. Holland, G. J. Bullen, Dylla Hosking, B. M. Roberts, D. Manson.

TILDEN LECTURE.

After a brief introduction, the President called upon Professor F. S. Dainton to deliver the Tilden Lecture entitled, " Atoms and Radicals in Aqueous Solution."

At the conclusion of the lecture, a vote of thanks to Professor Dainton, proposed by Dr. W. A. Waters, was carried with acclamation.

OFFICIAL ANNOUNCEMENTS

DEATHS.

The Council regret to announce the deaths of the following Fellows:

	Elected.	Died.
George Henry Carter (Bridlington)	Feb. 18th, 1926.	Jan. 11th, 1951.
George Dunn (Welwyn Garden City)	July 27th, 1945.	Jan. 26th, 1951.
Henry James Hodsman (Leeds)	Dec. 7th, 1911.	Jan. 31st, 1951.
Alexander Henry Mitchell Muter (S.E.11)	Dec. 3rd, 1896.	Feb. 7th, 1951.
William Charles Wilson (Stockport)	Aug. 17th, 1944.	Nov. 24th, 1950.

CONGRATULATIONS.

(a) *60 years of Fellowship.*

The President has conveyed the congratulations of the Society to Sir Thomas Kirke Rose (Hindhead), who completed 60 years of Fellowship on February 19th, 1951.

(b) *50 years of Fellowship.*

Congratulations have also been conveyed to the following who completed 50 years of Fellowship on February 7th, 1951 :

Sir Robert Waley Cohen (S.W.3).
Robert Dodd (Amberley).
Frederick George Donnan (Sittingbourne).

ELECTION OF NEW FELLOWS.

The following 96 candidates were elected Fellows of the Society on February 15th, 1951 :

Syed Mohsin Abbas.
Joseph Frederick Allen.
Fidel Jorge Lopez Aparicio.
Michael John Avery.
Alfred Edwin Philip Baigent.
Peter William Cecil Barnard.
Charles Stalley Barnes.
Sidney Charles Barnes.
Samuel Thomas Bebbington.
Harry Beck.
Ernest I. Becker.
John Harvey Binks.
Marjorie Linda Bird.
Roland Gordon Booth.
Warren John Brehm.
Frank Jefferson Broughton.
Archibald Peter Brown.
Joseph Lionel Burns.
Ernst Boris Chain.
Maurice Anthony Champney.
Antony William Thomas Cleaver.
James Clinch.
Gerald Cohen.
Adrian Maxwell Cook.
Archibald Stewart Cook.
John Richard Cracknell.
Edwin George Barton Crundwell.
Martin Craven Dawson.
John Farquhar Young Dick.
Donald Duxbury.
Brian Daysh England.
Kenneth Everett.
Joseph Harold Ewence.
Brian William Fox.
Alan John Fudge.
Harlan L. Goering.
Frederick D. Greene.
Erling Grovenstein, jun.
Edgar Harding.
Alfred Stanley Harris.
Kenneth Harrison.
William Wasney Heseltine.
Richard Keith Hill.
Kenneth Alan Henry Hooton.
Trevor Graham Hoyle.
Arthur William Ingersoll.
Siegfried Michael Jaeckel.
Leslie George Johnston.
Werner Robert Jondorf.
Chandrakant Kanekar.
James Jackson Kay.
George Kendall.
Vivian Yomtob Labaton.
Nelson Jordan Leonard.
John Barry Ley.
Thomas Herbert Liddicoet.
Terence Patrick McLaughlin.
Allison Maggiolo.
Leon Mandell.
Thomas David Manly.
Md. Asadullah Mehkari.
Roy Leander Milde.
David George Dickson Morrow.
Earl Leonard Muetterties.
Don Chandrasena Munasinghe.
Alec Clifford Nicholas.
Patrick Noel O'Donoghue.
George Arnold Officer.
Czeslawa Pajak.
Donald Frederick Parsons.
Deryck Stanley Percival Patterson.
Arthur Page Phillips.
James Stephen Pizey.
Yeshayau Pocker.
Robert Clive Poller.
Sylvia Joy Pugh.
Henry Rapoport.
William Eric Rhodes.
David Gerhardus Roux.
Norman Vine Saxton.
Binayendra Nath Sen.
Leslie Philip Seyb.
George Bernard Shapiro.
Helen Sophie Davidson Simpson.
John Valentine Smart.
George Boraston Smith.
Norman O. V. Sonntag.
Alan Gore Thompson.
Michael Edwin Trevett.
Donald Edward Trucker.
Peter Hermanus Van Roon.
Ernst Benedict Vischer.
Arthur Ernest Wain.
James Stoddart Watson.
Derek Farnham Williams.
George Martin Wyman.

RESEARCH FUND.

A meeting of the Research Fund Committee will be held in May next.

Applications for Grants, to be made on forms obtainable from the General Secretary, must be received on or before May 1st, 1951. Applications from Fellows will receive prior consideration.

Attention is drawn to the fact that the income arising from the Donation of the Worshipful Company of Goldsmiths is principally devoted to the encouragement of research in Inorganic and Metallurgical Chemistry, and that the income from the Perkin Memorial Fund is to be applied to investigations relating to problems connected with the Coal Tar and Allied Industries.

LONGSTAFF MEDAL 1951.

The Longstaff Medal for 1951 has been awarded to Professor C. K. Ingold of University College, London.

CORDAY-MORGAN MEDAL AND PRIZE.

The Corday–Morgan Medal and Prize for 1949 has been awarded to Dr. D. H. R. Barton of Birkbeck College, London.

The Award, consisting of a Silver Medal and a monetary Prize of 150 Guineas, is made annually to the chemist of either sex and of British Nationality who, in the judgment of the Council of the Chemical Society, shall have published during the year in question, the most meritorious contribution to experimental chemistry and who shall not, at the date of publication, have attained the age of thirty-six years. The Council has power to suspend the award in any year in which no suitable candidate presents himself or is brought to the notice of the Council.

Copies of the rules governing the Award may be obtained from the General Secretary of the Society. Applications or recommendations in respect of the Award for the year 1950 must be received not later than December 31st, 1951, and applications for the Award for 1951 are due before the end of 1952.

MEMBERS OF COUNCIL.

Mr. R. P. Bell has been co-opted as an additional Member of Council, under Bye-Law 19, from the date of his retirement from the Office of Vice-President on March 21st, 1951, for the period of his service as one of the Society's representatives on the Chemical Council.

MR. H. J. MORRIS.

At the Meeting of Council held on February 15th, the President, on behalf of past and present Members of Council, presented a cheque to Mr. H. J. Morris, the Society's Accountant, on completion of 40 years' service with the Society.

LOCAL REPRESENTATIVE—OXFORD.

The resignation of Dr. W. A. Waters as Local Representative for Oxford, as from the date of the Annual General Meeting, was accepted with regret, and Dr. H. M. N. H. Irving has been appointed as his successor.

BUREAU OF ABSTRACTS.

The Bureau of Abstracts regrets the delay in the issue of **British Abstracts** caused by the recent dispute in the printing trade. Every effort is being made to overtake the arrears, and, for the time being, issues will be distributed as soon as they are available, so that it is possible that all three parts of the " A " Abstracts may not be received by Fellows at the same time.

MEETINGS OUTSIDE LONDON

Centenary Lecture, " The Structure and Enzymatic Breakdown of Proteins," by Professor Dr. K Linderstrøm-Lang (Copenhagen).

This lecture was delivered in London on January 18th and in Sheffield on January 15th, Leeds on January 16th, and Newcastle on January, 22nd, 1951.

BIRMINGHAM.

" The Structure of Recently Isolated Timber Extractives," by Professor F. E. King, M.A., D.Phil.

A joint meeting with the University Chemical Society was held in the Chemistry Lecture Theatre of the University on January 26th, 1951, with Professor M. Stacey in the Chair.

After referring to the classification of commercial timbers, Professor King described the work in hand at the Nottingham University Laboratories on the isolation of natural products from timbers, principally hardwoods, resistant to fungi and insect parasites. The Lecturer described the chemistry of chlorophorin isolated from iroko (*Chlorophora excelsa*), of baikiain, an extractive from Rhodesian teak (*Baikiaea plurijuga*), and of a new lignan from the yew (*Taxus baccata*).

After some discussion, a vote of thanks to Professor King, proposed by Dr. W. G. Overend, was carried with enthusiasm.

EDINBURGH.

" Application of Exothermic Solid Reactions to Jet Propulsion and Industrial Purposes," by Dr. J. Taylor.

A joint meeting with the University Chemical Society, the Royal Institute of Chemistry, and the Society of Chemical Industry was held in the Lecture Theatre of the University Department of Physiology on February 6th, 1951, with Mr. A. V. Parke in the Chair.

The lecture was illustrated by many striking experiments, and at the end an appreciative audience carried with enthusiasm the vote of thanks moved by Mr. A. W. Henderson.

SHEFFIELD.

" Catalysed Oxidations," by Professor C. E. H. Bawn, Ph.D.

A meeting was held in the Chemistry Lecture Theatre of the University on February 1st, 1951, with Professor R. D. Haworth in the Chair.

After a brief survey of trace-metal catalysis in inorganic oxidations by molecular oxygen, Professor Bawn devoted the remainder of his lecture to the kinetics of the oxidation of aldehydes when catalysed by cobaltic ions. A vote of thanks, proposed by Dr. P. A. H. Wyatt, was heartily endorsed by the audience.

SOUTHAMPTON.

" Neutron Diffraction by Crystals," by Professor Kathleen Lonsdale, F.R.S.

A joint meeting with the Mid-Southern Counties Section of the Royal Institute of Chemistry and the Physical and Chemical Societies of University College, Southampton, was held in the Physics Department of University College, Southampton, on January 26th, 1951, with Mr. R. E. Parker in the Chair.

Professor Lonsdale gave a lucid and interesting account of the theory and practice of neutron diffraction and showed the usefulness of this new technique in dealing with such problems as the positions of the hydrogen atoms in ice, and the structures of ferromagnetic and antiferromagnetic substances. The lecture was illustrated by numerous slides and an ingenious model of the O–H–O bonds in ice was demonstrated.

After the discussion, a very hearty vote of thanks was accorded to Professor Lonsdale on the motion of Professor N. K. Adam.

PAPERS RECEIVED

(List of papers received between January 19th, 1951, and February 16th, 1951.)

" Amino-acids and peptides. Part III. The solubility criterion of chemical purity with special reference to amino-acids. The use of differential vapour-pressure measurements." By I. W. Hughes, E. W. Williams, and G. T. Young.

" Deoxy-sugars. Part XIX. The conversation of D-arabinose into 3-deoxy-D-xylose derivatives." By R. Allerton and W. G. Overend.

" Attempts to find new antimalarials. Part XXX. The synthesis of derivatives of quinolo(4′ : 3′-2 : 3)quinoline." By W. O. KERMACK and (MRS.) N. E. STOREY.
" The carbon–sulphur fission in thioethers. Part I. The retarding influence of α-methyl groups and of the length of the acid chain on the alkaline hydrolysis of α-(β-ketothio)- and α-(*p*-nitrotriphenylmethylthio)-acetic acids." By Y. ISKANDER and R. TEWFIK.
" The carbon–sulphur fission in thioethers. Part II. The retarding influence of α-methyl groups or the length of the acid chain on the alkaline hydrolyses of α-(nitrobenzylthio)acetic acids." By Y. ISKANDER and Y. RIAD.
" The carbon–sulphur fission in thioethers. Part III. The retarding influence of the length of the radical chain and of a second α-thioacetic acid group on the alkaline hydrolysis of α-(nitrobenzylthio)- and α-(nitrodiphenylmethylthio)-acetic acids." By Y. ISKANDER and A. SALAMA.
" The effect of particle size and deuterium substitution on the lambda-point in ammonium chloride." By D. G. THOMAS and L. A. K. STAVELEY.
" Anhydrocarboxy-derivatives of hydroxy- and mercapto-acids." By W. H. DAVIES.
" Nitrosoacylarylamines. Part V. The nitrosation of 3-acetamido-4-quinolones and -quinaldones." By (MRS.) W. J. ADAMS and D. H. HEY.
" The formation of ammonium amalgam by electrolysis." By R. J. JOHNSTON and A. R. UBBELOHDE.
" Synthesis of possible antimalarials. Part II. Compounds with the *iso*quinoline ring attached to the quinuclidine system." By G. R. CLEMO and S. P. POPLI.
" Oxidation of organic compounds by nitrous oxide. Part I." By F. S. BRIDSON-JONES, G. D. BUCKLEY, L. H. CROSS, and A. P. DRIVER.
" The oxidation of organic compounds by nitrous oxide. Part II. Tri- and tetra-substituted ethylenes." By F. S. BRIDSON-JONES and G. D. BUCKLEY.
" Oxidation of organic compounds by nitrous oxide. Part III. Acetylenes." By G. D. BUCKLEY and (MISS) W. J. LEVY.
" Eight- and higher-membered ring compounds. Part IV. Di-*m*-xylylene, tri-*p*-xylylene, and new syntheses of pyrene, and of coronene." By WILSON BAKER, J. F. W. MCOMIE, and MISS J. M. NORMAN.
" Eight- and higher-membered ring compounds. Part V. Di-(2 : 7-naphthylidenebismethylene) and its conversion into coronene." By WILSON BAKER, F. GLOCKLING, and J. F. W. MCOMIE.
" Esterification by dinitrogen tetroxide." By A. D. YOFFE and PETER GRAY.
" Chemistry of New Zealand *Melicope* species. Part VII. Some observations on the relation between the constitution of some flavonol derivatives and their acidity, basicity, colours with ferric chloride, and ultra-violet absorption spectra." By L. H. BRIGGS and R. H. LOCKER.
" The action of ionizing radiations and of radiomimetic substances on deoxyribonucleic acid. Part IV. The products of the action of di-2-chloroethylmethylamine." By K. A. SMITH, E. M. PRESS, and J. A. V. BUTLER.
" Toxic factor from agenized proteins : infra-red measurements." By L. N. SHORT and H. W. THOMPSON.
" Unsaturated lactones and related substances. Part V. β-Ketodihydromuconic acid and carboxy-lactones of the protoanemonin type." By U. EISNER, J. A. ELVIDGE, and R. P. LINSTEAD.
" Triterpenoids. Part III. *cyclo*Artenone, a triterpenoid ketone." By D. H. R. BARTON.
" On the spreading of monolayers of myosin." By A. LATHA and E. K. RIDEAL.
" The reaction of α-bromobenzyl cyanide with ethylxanthamide." By W. DAVIES and J. A. MACLAREN.
" 4 : 5-*iso*Propylidene 1 : 2-3 : 6-dianhydromannitol." By A. B. FOSTER and W. G. OVEREND.
" Anodic syntheses. Part IV. Synthesis of (+)- and (−)-tuberculostearic acids." By R. P. LINSTEAD, J. C. LUNT, and B. C. L. WEEDON.
" Amidines. Part XVI. A new synthesis of 1-alkyl- and 1-aryl-3 : 4-dihydro*iso*quinolines." By C. I. BRODRICK and W. F. SHORT.

"The kinetics of the dissolution of zinc in aqueous iodine solutions. Part II." By L. L. Bircumshaw and A. C. Riddiford.

"A theoretical treatment of the Diels–Alder reaction. Part III. Equilibria for aromatic hydrocarbons." By R. D. Brown.

"The synthesis of 5- and 7-methoxytryptophan, and of some derivatives." By R. H. Marchant and D. G. Harvey.

"The ultra-violet absorption spectra of mercurous perchlorate solutions." By W. C. E. Higginson.

"The constitution of a pear cell-wall xylan." By S. K. Chanda, E. L. Hirst, and E. G. V. Percival.

"The structure of pyrid-4-thione." By I. G. Ross.

"Chemical actions of ionising radiations in solution. Part IX. Radiation chemistry of sterols. The action of *X*-rays on œstrone in aqueous solutions." By M. Keller and J. Weiss.

"The synthesis of piperidine derivatives. Part V. Decahydro*iso*quinolines." By G. M. Badger, J. W. Cook, and G. M. S. Donald.

"Studies in the sterol group. Part LI. Reactions between 17-keto-steroids and organometallic compounds." By C. W. Greenhalgh, H. B. Henbest, and E. R. H. Jones.

"The preparation of 1-bromo-2-methylnaphthalene." By D. M. Hall and R. K. Mitchell.

"The chemistry of the *Mitragyna* genus. Part II. Synthesis of 7-methoxy-2-methyl- and 7-methoxy-1 : 2-dimethyl-β-carboline." By J. W. Cook, J. D. Loudon, and P. McCloskey.

"The reaction between aromatic compounds and derivatives of tertiary acids. Part VI. The simultaneous formation of open-chain and cyclic ketones from some alkylated, phenylpropionyl chlorides." By E. Rothstein.

"Monosubstituted pyrimidines and the action of thiourea on chloropyrimidines." By (Miss) M. P. V. Boarland and J. F. W. McOmie.

"The salting-out of non-polar compounds. Part I." By T. J. Morrison and F. Billett.

"A new synthesis, and the chemical properties, of 5-aminopyrimidine." By N. Whittaker.

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"Thermal interchange of acyl groups in triglycerides." By C. Barker, R. V. Crawford, and T. P. Hilditch.

"The electrochemistry of boron trifluoride co-ordination compounds. Part II. Boron trifluoride-mono(acetic acid)." By N. N. Greenwood, R. L. Martin, and H. J. Emeléus.

"Quaternary ammonium salts. Part II. The formation and decomposition of diethylmethylanilinium salts. Another route for the synthesis of *N*-ethyl-*N*-methylanilines." By H. A. Fahim and A. M. Fleifel.

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"The kinetics of exchange reactions. Part IV. Substituted phenyl and benzyl bromides." By (the late) S. Sugden and J. B. Willis.

"The seed oil of *Onguekoa gore* Engler. Part I. The position of the hydroxyl group in the unsaturated monohydroxy-C_{18} acid (or acids)." By J. P. Riley.

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"Alkenylation employing lithium alkenyls. Part V. The formation of *cyclo*pentenyllithium. Syntheses and oxotropic rearrangements in the *cyclo*pentenyl series. (Studies in molecular rearrangement, Part VII.)." By E. A. BRAUDE and W. F. FORBES.

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